Transcript of January 10, 2002 Meeting

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HEALTH CARE FINANCING ADMINISTRATION
Medicare Coverage Advisory Committee
Meeting of the Diagnostic Imaging Panel

January 10, 2002

Baltimore Convention Center
One West Pratt Street
Baltimore, Maryland

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Panelists

Chairperson
Frank J. Papatheofanis, MD, PhD, MPH
Vice-Chairperson
Barbara J. McNeil, MD, PhD

Voting Members
Carole R. Flamm, MD, MPH

Jeffrey C. Lerner, PhD
Steven Guyton, MD
Kim J. Burcheil, MD

Consumer Representative
Sally Hart, JD

Guests
Marilyn Albert, PhD
Keith Johnson, MD
Peter Neumann, ScD

CMS Liaison
Sean R. Tunis, MD, MSc
Executive Secretary
Janet Anderson

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PANEL PROCEEDINGS

(The meeting was called to order at 8:35 a.m., Thursday, January 10, 2002.)

MS. ANDERSON: We're going to get started now. Good morning and welcome committee chairperson, members an guess. I am Janet Anderson, executive secretary of the Diagnostic and Imaging Panel of the Medicare Coverage Advisory Committee, known as MCAC. The panel is here today to hear and discuss presentations from interested persons regarding the use of positron emission tomography, known as PET scanning technology for the diagnosis and patient management of Alzheimer's Disease and other dementias.

In evaluating the evidence presented to you today, CMS encourages the committee to consider all relevant forms of information including but not limited to professional society statements, clinical guidelines and other testimony you may hear during the course of this committee meeting. The following announcement addresses conflict of interest issues associated with this meeting and is made part of the record to preclude even the appearance of impropriety. The conflict of statutes prohibit special government employees from

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participating in matters that could affect their or their employers' financial interests. To determine if any conflict existed the Agency reviewed all financial interests reported by the panel participants. The Agency has determined that all members may participate in the matters before the panel today.
With respect to other participants, we ask in the interest of fairness that all persons making statements or presentations disclose any current or previous financial involvement with any firm whose products or services they may wish to comment on. This includes direct financial investments, consulting fees and significant institutional support.
I would now like to turn the meeting over to Dr. Sean Tunis, who will give his opening remarks. Then Chairman Dr. Frank Papatheofanis will ask the committee members to introduce themselves and to disclose for the record any involvement with the topics to be presented. Dr. Tunis.
DR. TUNIS: Thanks, Janet. First, I just wanted to thank all the panel members for being here today and for I'm sure the hours and hours they have spent reading over the material that has been

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provided to them. I wanted to assure everyone that we're aware that this is one of the more analytically complex issues that has been faced by an MCAC panel

so we look forward to the discussion and teasing all these issues apart in this setting. Again, thanks for your hard work in preparing for this.
The other comments I wanted to make relate to the issue of some of the folks on this MCAC committee as well as others have been increasingly frequently contacted by various advocates and stakeholders related to specific issues coming before the MCAC committee, so we wanted to clarify in public what the views of CMS are related to advocates related to MCAC members on topics that are coming before the panel.
And basically I just have a few points to make on this, which is the whole point of MCAC is that it's a FACA compliant committee, meaning that the business of information exchange related to topics coming before MCAC should be made ideally in public and as close to 100 percent of information exchange that can be done in the settings of public meetings is what's ideal, so we are discouraging substantive conversations between MCAC members and advocates or stakeholders related to the issues.

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Kind of in the same vein, you all as MCAC members are special government employees of CMS only for the time that you actually spend here and therefore, if you're just having discussions in advance of this with advocates, you're doing that on your own time but not as representatives of this committee and you are obviously free to spend your own professional time however you want, so there is no way for us to explicitly preclude you from having those conversations with the advocates or lobbyists. However, again, just to remind you that you're only special government employees for the time that you're here, and I'm sure you're aware of that because you only get one small pay check.
And the last point is that we won't be doing it today, but from here forward at all MCAC meetings we will be asking at the beginning of the meeting for you all to disclose in addition to any conflicts of interest to simply disclose whether you

have been contacted and have had any discussions with any stakeholders relating to the technology under question, simply to identify who the individual is and who they represent. And that's really a way of just making sure that if you have had contact with folks, that is made publicly known so that can be

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factored into any subsequent comments that you may have. So we will be doing that hence forward but since we haven't formally announced the policy of that type before this, we won't be doing that today. Those are my introductory comments. I don't know if anyone has any questions about those, our approach to lobbying, but you can either raise them now or anytime later in the day. With that I will turn it over to Frank.

DR. PAPATHEOFANIS: Thank you. I would also like to add my welcome to the panel members and basically highlight especially the contributions of folks who haven't participated before as panel members but who have made a very meaningful contribution to our efforts. That includes Dr. Albert, Dr. Neumann and Dr. Johnson, and before any of us forgets, I would like to acknowledge their meaningful contribution hopefully to today's discussions.

All of you have an agenda before you and I would like to emphasize that we will adhere to this agenda just as closely as we can. In fact, I've got about a minute before we start the 8:45 presentation by Samantha Richardson.

In keeping with Sean's request on

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disclosure, let me start by introducing myself and my potential conflicts, if you will, and then we will go around and introduce everyone and if they can let us know if there is anything along those lines. I am a practicing nuclear medicine physician on the faculty of the University of California at San Diego, and I would be someone who uses PET imaging in my clinical practice. My position at the university is such that

the university does do business with all of the vendors that are involved in the manufacturing of the PET imaging technologies that are being considered. Why don't we go down the line and start with Dr. Flamm.

DR. FLAMM: My name is Carole Flamm and I do not have any specific financial conflicts of interest related with PET. I am a diagnostic radiologist and I do technology assessment.

DR. GUYTON: I'm Steve Guyton. I'm a cardiac surgeon in Seattle and don't have any conflicts.

DR. BURCHEIL: I'm Kim Burcheil. I'm professor and chairman of the department of neurological surgery at Oregon Health and Science University in Portland. I don't have any conflicts and I have not been contacted by anybody.

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DR. ALBERT: I'm Marilyn Albert and I am director of the gerontology research unit at Mass General Hospital and professor at Harvard Medical School, and do a lot of research in the area of diagnosis of Alzheimer's Disease but don't have any particular conflicts with regard to the use of PET.

DR. NEUMANN: Peter Neumann. I am on the faculty of the Harvard School of Public Health and I also do research in this area with a background in decision analysis and cost effectiveness analysis. I have no conflicts and I was not contacted by anyone.

DR. McNEIL: I'm Barbara McNeil. I'm chairman of the department of health care policy at Harvard Medical School. I do clinical work in the nuclear medicine division at the Brigham and Women's Hospital one day a week and in that context read PET studies, but have no other involvement.

DR. LERNER: I am Jeff Lerner. I am president of ECRI and I direct our evidence based practice center designated by AHRQ. I have no conflict of interest and have not been contacted prior to the meeting.

DR. JOHNSON: I am Keith Johnson. I am a neurologist at Brigham and Women's Hospital and

Harvard Medical School, and I have no conflicts.

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MS. HART: I am Sally Hart. I am an attorney with the Center for Medicare Advocacy. I am the consumer representative on the panel and I have no conflict of interest.

DR. PAPATHEOFANIS: Thank you. Why don't we get started then, and I will ask us to kick off the day with a presentation by Samantha Richardson. Welcome.

MS. RICHARDSON: Thank you. Good morning, members of the panel, invited guests, members of the public and press. My name is Samantha Richardson. I am the project lead for this topic at CMS. Today we are asking the panel to review and render a recommendation regarding the usage of PET in the evaluation of patients with suspected AD. As an introduction to the subject I will begin by recapping the history of this coverage request. I will also review the general discussion questions and voting question that we posed to the panel. At the conclusion of my presentation I will introduce Dr. Deborah Zarin, of the Agency for Healthcare Research and Quality.

Before you is the time line of the chronology of this coverage request. Back in July of 2000 we received a formal request from UCLA for broad

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coverage for positron emission tomography using FDG. In November we discussed it, CMS discussed the issue with the Executive Committee and they recommended further analysis. In December 2000 after a decision was made on the initial request there were certain indications that required further analysis so we then referred it to an MCAC panel. In May of 2001 CMS requested a technology assessment by AHRQ. We then had a meeting in July to get more information from the Executive Committee as to how to frame our analytical questions for the technology assessment. In August of 2001 AHRQ selected the Center for Clinical Health Policy Research at Duke

University as the evidence based practice center for the technology assessment. In October 2001 we received a formal amendment to the initial coverage request by UCLA and in December we received the technology assessment from AHRQ, which brings us to today.
CMS has given all the panel members the same information, which includes the agenda, the amended request from UCLA, the technology assessment, discussion and voting questions, and background articles. The background material consists of the American Academy of Neurology guidelines, articles

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submitted by AHRQ on decision modeling, as well as all of the articles submitted by UCLA.
I will briefly discuss or review the panel questions that we have posed.
Question number 1. Is using the AHRQ decision model, including its assumptions and calculations, a reasonable way to determine the clinical utility of PET as an imagining tool in the diagnosis and management of Alzheimer's Disease? If so, are there specific groups of patients who might benefit from receiving a PET scan following a standard clinical evaluation for suspected AD?
What other issues, which have not been addressed in this model, might influence the decision to use PET in the evaluation of patients with suspected AD?
Could PET serve as a replacement for, rather than simply an adjunct to, certain components of the conventional clinical evaluation for suspected AD?
And finally, the voting question: Is the evidence adequate to demonstrate that PET has clinical benefit in evaluating patients with suspected AD?
I thank you in advance for your review and

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discussion of the topic and at this time I would like to invite Dr. Deborah Zarin from AHRQ to the podium.

She will present in greater detail on Alzheimer's Disease as well as give an overview of the technology assessment.
DR. PAPATHEOFANIS: Thank you, Miss Richardson. She did a great job of giving us an overview of what this panel will be considering today, and I want to call your attention to the one-page document you have all received that's addressed CMS Questions for January 10, general discussion questions. Basically what you have just heard is a very short overview of what we're going to be doing, but the bottom line is the charge to the panel is really the voting question you see at the bottom of that page, and basically we are charged with, this panel is charged with evaluating the evidence and at the end of the day taking a vote that will serve to guide CMS in their consideration of coverage for this technology.
So, if there aren't any questions at this point we will just continue with Dr. Zarin and her summary of the technology assessment.
DR. ZARIN: Keep talking.
DR. PAPATHEOFANIS: Keep talking? Sure.

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I feel that we should, with all of the Harvard and Brigham people here, we should have met in Cambridge instead of Baltimore today, but I'll keep that to myself, Barbara. I have no other humor.
(Laughter.)
DR. PAPATHEOFANIS: There is one thing on a serious note. We will try to expedite this agenda today and if we can, we want to get people out to the airport as soon as we can this afternoon. I know that there's folks who have flights starting as early as 3:00 p.m., and I think especially for folks who are traveling great distances, it will behoove us all to stick to the schedule and really be very aggressive although focused in what we discuss.
So, Dr. Zarin.
DR. ZARIN: Thank you. What I'm going to do is really ease you into the mindset necessary to hear Dr. Matchar's presentation of the technology

assessment, so we will go briefly over some key features of the disorder, the treatments and the model.
The key features of AD, I guess if any of you don't know this by now, then we should go home, but it's a progressive neurodegenerative disease, the incidence increases with age, and it's one of several

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causes of dementia, accounting for approximately two-thirds of cases, obviously depending on how you choose your sample.
You're going to see I'm sure other slides today with more details about the standard diagnostic workup for AD, these are drawn from the American Academy of Neurology guidelines, but basically at the current time you're getting history and physical exam, neuropsych evaluation, screening laboratory tests, structural neuroimaging, and that's important to note because we have not evaluated PET as a replacement for the structural neuroimaging that's part of the initial workup and it hasn't been suggested as far as I know that it would be a useful tool at that point in the workup.
And then the last bullet is observation of course either with or without treatment or with or without diagnosis, but clearly ongoing observation and care of these patients is necessary whether or not you have definitively diagnosed them as having AD at the beginning. And that's an important point because occasionally you will hear arguments that if only you could diagnose them then you wouldn't have to keep following up, but clearly these people need to be cared for whether or not they have a definitive

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diagnosis.
So how would you look at the potential role of PET? And this is one of the slides that I used in talking to the Executive Committee in the spring. The concept is that if you could have an earlier diagnosis of AD or another cause of dementia, you could institute treatment earlier, and that would

lead to better health outcomes. It's a fairly simple concept but that's kind of where we're coming from here.

So we're thinking about PET as a diagnostic test, and the MCAC Executive Committee has guidelines for evaluating diagnostic tests. And the first thing that they want to look at is what's the evidence regarding the accuracy of the test. And implied in that is compared with other standard methods of diagnosis, that's the only way to really look at accuracy, compared to what.

The second set of information that they are asking us to look at is evidence regarding the impact of improved accuracy on health outcomes. So the concept here is that just having improved accuracy isn't necessarily good enough, you want to know, does the improved accuracy actually help the patient and how.

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So these were some cartoon-like decision trees that I showed in the spring. Here's the first concept, that patients could be diagnosed using PET scan and the treatment would then be dependent on the results of the diagnosis. You don't have to look at the details here. Then you could make a decision whether to treat or not to treat depending on either the results of the PET scan or the results of the clinical workup if they didn't have a PET scan. And then patients could have an outcome, and the types of outcomes you could see is either no change in cognitive status, a slower progression, or the typical progression that you would expect if there were no treatment.

So let's think about this for a second. This is a threshold approach, those of you who are decision analysts will be familiar with this, but the horizontal axis is a probability scale from zero to one and it's the probability of having Alzheimer's Disease. So over on the right you have a probability of one of having Alzheimer's Disease, which means we are absolutely certain that you have Alzheimer's Disease, and over on the left a probability of zero,

we're absolutely certain you don't. And you can imagine that given that, and we will go through a

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little bit about the data, there's data showing that there are treatments that are effective, that if you were absolutely certain that someone had Alzheimer's Disease you would treat them; if you were absolutely certain that they didn't have Alzheimer's Disease, way over on the left, you wouldn't treat them.
Somewhere there is what we call a treatment threshold. We don't know what that probability is exactly, but somewhere there is a probability above which you're certain enough that you would treat and below which you're uncertain enough that you wouldn't treat. And where that threshold is depends on a lot of things, and one is the features of the treatment, in particular the beneficial and adverse effect, as well as the patient's utilities.
So that's one way of thinking about the diagnostic test is, does it move you along that horizontal axis enough to get you from the part that says don't treat to the part that says treat. So you don't have to be certain, you don't have to have a probability of one to think that you should treat someone and in medicine we hardly every have a probability of one. And you don't have to have a probability of zero to say don't treat, but somewhere

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in there you might think about a threshold. That's just a conceptual model to think about while you're hearing the details.
So in order to actually analyze this problem you need to specify a few things, who are the patients we're talking about, what are the treatments, and what are the outcomes of interest.
So you can't go any further without specifying those things. So for patients, this is a slide that I had shown in the spring. You can imagine, you could start at the top, the blue square, all patients over 65 years old. Are we talking about that, are we

talking about the subset that are concerned due to a decrease in memory or other reason? In this case the other reason might be a family history of Alzheimer's Disease. Under there there's a subset of those who mentioned those concerns to a physician or other healthcare provider. There's a subset of those who were referred for workup because of signs or symptoms or family history. There's a subset of those who are actually shown to have dementia on clinical workup but you still don't know what the cause of the dementia is. Some of those have AD highly suspected, and some of those have AD.
So the question is, who are we talking

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about here, and it's important to think about. It has big implications both for the analysis of the data as well as obviously the quality of healthcare that's given later on. So in doing this analysis and looking into the literature and talking to experts, we actually decided to analyze separately, we took that big spectrum that I showed you and categorized it into three discrete groups, and this was based on groups that have been most talked about as potentially benefitting from getting a PET scan, and we thought it was important to distinguish among them because the issues are slightly different.
So the first group are people with mild to moderate dementia, so you know they have dementia and it's in the mild to moderate range. AD is suspected, but there is no way to confirm it, and the question is, would this group benefit from a more certain diagnosis? Would this group benefit from basically moving them on the probability scale further to the right from some test that could say you're here and we're going to move you over, push you over to the right because this test can tell you. So that's what we call scenario A when you read the technology assessment.
Scenarios B and C. Scenario B are

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patients with what's called mild cognitive

impairment, and that's described further in the technology assessment, but these are patients who have a lower score on standard dementia rating scales than people with clear dementia. They are not normal, they don't have the level of functional or cognitive impairment that you see in people who are clearly demented, and they are kind of in this state of it's unclear whether they are going to progress or not. And the question is, the reasonable question is, we have these medications that are currently being tested in drug trials in this group, one hypothesis is that the drugs are more effective the earlier you give them, so the question is, would it help to know which of these patients should get the medication. So that's scenario B.
Scenario C is patients with no symptoms at all, they are completely fine, but they have a family history of AD such that their probability based on genetic risk and epidemiologic data is elevated compared to another asymptomatic person. So they are at elevated risk but are currently asymptomatic. And again the question is, you know, you're somewhere on that probability scale, would it help your decision of whether to take medications to push you further to

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the right, to gain more certainty about your probability of getting AD is essentially what we're doing.
So for both B and C the question is would these patients benefit from a more certain diagnosis. Is it clear to the panel what we did with those three scenarios? Okay.
The treatments that we looked at. One of the problems or opportunities in doing this analysis is that it's a quickly evolving field, both the diagnosis tests are evolving and the treatments are evolving. There are lots of drug trials going on, lots of preliminary data, some confirmed data, and one of the advantages of doing a model like this is that you can use it to model what might be advances in the field, so a year from now if more data came in say about drug treatment and MCI, it could be plugged

into this model. But we wanted to develop a model that could be used not just for the drugs that we know work now but for say the next generation. So we used the acetylcholinesterase inhibitors which are the drugs that are currently confirmed to work best now in the patients with mild to moderate dementia. There are not yet confirmed data about these drugs in the other groups, but you

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can read more about that and I think Dr. Matchar will talk a little more about that. So we use them as the prototypes. It's important to note that the patients in the trials in which these drugs were tested were selected based on clinical diagnosis. This is an important point because it comes to, how you do know in whom these drugs are going to work? The only thing we know is that the patients selected the way they were selected in those clinical trials were essentially using the AAN clinical diagnosis guidelines and they were selected in that way. And they were shown that the patients who were thought to have AD based on that showed some benefit, and the benefit was slowing of progression. There is not a drug out there that we know of that cures the disease and we're not talking about preventive measures either at this point, so we're talking about a group of drugs that have been shown to slow the, on average, to slow the progression when given to people with mild to moderate dementia. And again, a note that practice guidelines for the treatment of patients with Alzheimer's or dementia recommend medication as part of the comprehensive treatment approach. Again, it's not as if once you

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know they have Alzheimer's, you mail them the pills and say call me in ten years. These patients need ongoing care whether or not you're still reevaluating the diagnosis, because again, that issue comes up. The medication is part of the treatment package, has been shown to slow progression.

Outcomes. Again, another point to remind you, that the MCAC has made it clear that just the change in patient management is not a sufficient outcome to show the benefit of a diagnostic technology. So again, the argument that well, we did PET scan on a hundred patients and this changed our decision in 70 of them, and therefore it's a good test, isn't good enough. The question is were those 70 -- well, were the whole hundred on average better off because they got that diagnostic test.
So what are the outcomes that we looked at? LE stands for life expectancy, how long did the patients live under the different strategies? Quality adjusted life years. And then we added one called severe dementia free life expectancy. Some people would argue that there is sort of an ethical and philosophical question, if you will, of whether prolonging the stage in which you're in severe dementia is actually a benefit, but it's clear that

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prolonging the phase of your life before you get to severe dementia is a benefit. So we looked separately at how many more months or years of life you have prior to getting to the severe dementia state. So that's the, I think it's abbreviated SDFLE in your technology assessment.
So summary, so we looked at three patient populations, those with mild to moderate dementia, those with MCI, those who were asymptomatic but have a family history. We looked at the treatments using acetylcholinesterase inhibitors as the prototype, and looked at basically three outcome measures.
Now, what would be the ideal evidence we would have? The ideal evidence would come from a randomized controlled trial that randomized people who had suspected mild dementia, suspected AD, to get a PET or not get a PET. They would all get the standard workup and in addition, some would get a PET scan, some wouldn't. Based on that you'd make your treat or no treat decision and you'd follow them for outcomes. And then you could say definitively after X number of years, the group with the PET scan did or

didn't do better than the group without the PET scan. So that would be what we'd like, and we didn't have it.

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That trial hasn't been done, so we developed a model, okay? And you have heard some about this, but the point of the model is that it gives you a mechanism for combining data regarding diagnostic accuracy, because there are clinical trials looking at the diagnostic accuracy of the PET scan; treatment trials looking at treatment efficacy, and what we know about patient management decisions to determine possible outcomes. So it lets you combine in a way those three types of information into a model, let's you do it in an explicit way that we can all argue about whether it makes sense or not. You can see which way you believe and you can in fact as the next bullet says, you can do a sensitivity analysis for many of these, which is really asking the what-if question, what if you know, Dr. Lerner and I disagree about one of the numbers? Well, we can say okay, would this make a difference in the outcome, you know, do we think this was a rational way to do it. And so it lets you model the effects of uncertainty in the data but also, and this is important I think for this topic, potential advances in the field. So you can say what if, you know, I know that in three months some drug trial results were coming out that showed it to be twice

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effective as what we know about now, would that change the conclusions, and you can model that and look at that. So that's the reason for doing the model.

Now I'm going to pass it on to Dr. Matchar, but does anyone have questions about the basic approach?

MS. ANDERSON: Thank you.

DR. MATCHAR: Good morning. Now this presentation was a challenge for me because it's an effort to summarize in some sense a technology

assessment that was fairly complicated and academically derived. It's very important I understand here to try to take that material and to convert it into something that makes some sense to you and to the public. So I accept that challenge. Instead of reviewing the technology assessment in exquisite and painful detail, what I'd like to do is to give you an overview of the substance of that approach that we took, I think Dr. Zarin already gave a very nice overview as to why we approached it as we did, and describe the principal result and then also hopefully explain some of the insights and why these insights were derived from the model and the way they were.

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So the objectives of the analysis were to assess PET scanning in conjunction with standard evaluation of patients who have one of the three scenarios that were previously described by Dr. Zarin, individuals who already had dementia that was either mild or moderate, and specifically avoided patients with severe, although there is some evidence that individuals with severe dementia will benefit in some ways from treatment, we did focus on mild to moderate. We also looked at patients with mild cognitive impairment. Again, as Dr. Zarin pointed out, that's a group for which there is not evidence of treatment benefit to date but there is a clinical trial in progress. And then the third was patients with an elevated risk because of a family history of AD but who do not currently have symptoms. Again, evidence of treatment effectiveness is not available, but we did want to include this in order to assess the potential for diagnostic testing even in that circumstance. Again, the important issue here is not just whether the test is accurate and whether it properly partitions patients into true positives and false positives and so on, but rather, whether that partitioning leads to an improvement in health outcomes, and I will go into some detail about

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what we mean by health outcomes.
As pointed out already, the ideal circumstance would be that we would have direct evidence and would be able to make a direct inference from clinical trials that would allow us to say that testing leads to say delayed progression, decreased mortality or other useful outcomes that people care about. An analogy would be in the case of mammography, say, to do a clinical trial, and Dr. Zarin again pointed out what that trial would probably look like. There is no evidence available to us and so the challenge that we were presented with was needing to make an indirect inference about the potential that PET scanning might have in these circumstances.
Now this indirect inference can be made by establishing a causal pathway which is sort of the conceptual underpinning of the analysis that we did. The idea is that the testing leads to identification of people who are true positives, and I'll mention in a moment what we mean by true positives, because that's very much at the core of this analysis, understanding that concept. That those patients who are true positives are treated and that as a consequence of treatment they have delayed

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progression, and indirectly have decreased mortality. Again, no evidence that treatment directly decreases mortality although there is reason to believe that patients may have decreased mortality because they have diminished disability and therefore the associated mortality of disability.
Now, testing also has other potentially downsides. The test may be either a false negative or false positive. In the case of a false negative the test, the individual who has the disease fails to be treated and again, if treatment is useful, they fail to have that delayed progression. They may be a false positive. Again, in this circumstance, depending on whether the patient would have otherwise been treated in any case, they experience whatever downsides there are to treatment without achieving

any of the benefits. They may also be identified as a true negative in which case they are left alone appropriately. Treatment may have adverse events whether or not the patient actually has the disease. Now let me focus on this concept of a true positive. Because there are many different ways one could define what a true positive is in this context it's very important to have our demonstration straight, because all the subsequent analysis hinges

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on defining what we mean by disease. As Dr. Zarin pointed out -- well, first of all, let me go through the list of possibilities.
One possibility would be that we obtain histopathology on all patients and that would mean biopsying people's brains. That would be one possibility, unlikely possibility but one way of diagnosing disease. It might also be based on clinical diagnosis or it might be based on some other kind of test. Now for purposes of this analysis we used the diagnosis, the clinical definition, and there are two real reasons we did that. The first is just that that's what is the standard for diagnosis of Alzheimer's disease, namely the clinical evaluation as stipulated by the American Academy of Neurology guidelines.
But more importantly for this analysis, the treatment effectiveness has been studied based on this clinical definition. There has to our knowledge not been any evaluation of the benefit of drug treatment based on results of say PET scanning or other diagnostic methodology other than clinical evaluation. So that's really key, that being a true positive means being a true positive in the sense that this is a person who has been shown in clinical

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studies to benefit from treatment, whether on biopsy they ultimately prove to have Alzheimer's disease or not. That is a possibility.
Now in developing a model, again as pointed out already, that a model has several values.

In this circumstance, actually the only way we can make an indirect inference and actually calculate any of the things that we talk about being interested in, you know, that people care about, they care about life expectancy, they care about quality of life, dementia free survival and so on. In order to calculate those things in the absence of that ultimate clinical trial, it's really the only way, in the absence of that trial, developing a model is the only way to make these predictions.
It also allows us to integrate data from these various sources and there are some excellent sources say of the natural history of disease for example, the CRAD data which we used in this analysis. Treatment trials, there have been several fairly consistent treatment trials regarding the use of acetylcholinesterase inhibitors and there have been a good number of studies looking at test performance.
Now we initially were asked specifically

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to make sure we understood what the quality of the test performance is, and as we'll see in this analysis, the test performance itself is not that important; the sensitivity and specificity can be established to be quite good, or reasonably good, in a global sense. You know, the numbers for sensitivity and specificity are fairly high.
Now the model that we developed has two major parts. The first part relates to various strategies that would be used in, for testing or not testing and treatment. For example, we'll start with the scenario of an individual with mild dementia. Under this scenario in which they have a PET scan, they may in fact in truth have Alzheimer's disease, and that's based on what's the prevalence of Alzheimer's disease in that population. And they may based on testing be identified as being positive or not. And the likelihood that an individual who is, who has disease is going to be positive by the test is the sensitivity of the test.
So if an individual follows that top half,

they have mild dementia, they undergo PET scanning, they in fact, the omniscient knows that this person has Alzheimer's disease and in fact after testing are positive, that individual now has Alzheimer's disease

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and they are treated.
An individual following that second path in which they are actually a false negative, they don't get treatment although they do have disease.
So each of these branches has an associated diagnosis and then a subsequent management strategy implied.
And it's important to point out that there is a basic medical truism, which is one should not do a test unless one is going to base their treatment decisions on that test result, and that's why in this circumstance if the individual who comes in with mild dementia has a negative scan, they would not be treated. Otherwise, at least for purposes of the treatment decision, why did you do the test in the first place.
Now, another option for individuals with mild dementia is not to do the scan but at that point just to go on and treat them. One might call that empiric treatment but it's basically treatment based on the standard diagnosis, the standard clinical diagnosis. Again, there is a certain proportion of those people who have mild dementia who will have AD and they will be true positives and will go on to treatment and those who don't have AD will still get treatment. So that group of people are going to

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undergo unnecessary treatment with whatever downsides are associated with unnecessary treatment.
Now based on discussions with, based both on the evidence and also discussion with our experts who advised us in this project that in the case of the anticholinesterase inhibitors, with these drugs about 15 percent or so of patients will experience adverse reactions which are very limited in the sense that the worst thing that typically happens is that they stop the drug.

And then of course there is a possibility of just leaving a patient alone entirely and not bothering to test them or to treat them and in this case whether they have AD or don't have AD, they don't get treated.
Again, just reminding everyone of this notion that the test performance is that one of the biggest parts of this project was to identify test performance and we reviewed fairly extensively, or very extensively I should say, the literature regarding the performance of PET scans and a major challenge for us as I pointed out was figuring out how to construct two-by-two tables from this evidence, and all of the two-by-two tables we constructed and all the presentations we did for the

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most part were based on this paradigm, which is that diagnosis as you see on the top row, that the diagnosis was based on disease by clinical evaluation, and just to remind everyone that sensitivity is the proportion of people who have the disease, that is that middle column, of all those people in that column, the proportion who are true positives, and the specificity of all the people in the right column, all the people who are true negatives.
Again, without going into the painful detail about how the analysis was done, you can go back to the technology assessment to see all the machinations underlying this, but basically you can just pretend that we took all of the sensitivities and all the specificities and just averaged them, and despite the fact that this required several weeks of work, I had to show that to you, but basically the result would have been about the same, which is that the sensitivity and specificity of the tests were approximately 86, 87 percent, both, so that was our base case estimate of the sensitivity and specificity of PET scanning.
So the second part of the model now goes on and asks this question, okay, so what next, what

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about the fact that a person is identified as having disease and is treated or not treated, what happens then? So the foundation of the second part of the model is what we call the natural history model. And what the natural history model is is for want of a better expression, I'll call it a clinical trial in a box.

Basically we take individuals and we imagine that people exist in discrete health states and for purposes of this analysis these six health states are the important health states, that being asymptomatic, having mild cognitive impairment, having mild dementia, moderate dementia or severe dementia, or being dead, and that the arrows indicate the possible transitions people can make from state to state. And for the sake of simplicity, we assume these transitions can occur annually in a discrete fashion.

And again, going on with the, this is a general purpose natural history representation of a natural history that we could imagine that an individual starts in the asymptomatic state or in any of these other states, but for purposes of this preliminary baseline analysis I'm going to just talk about individuals starting with mild dementia.

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Now the arrows as I say, represent the transitions from state to state, but how likely are those transitions in any given year? Well, we can go to the epidemiologic data and we can sort out, again, there's the painful details in the report but we can sort out what the likelihood is from year to year that an individual would make that transition, and the likelihood of making that transition is going to depend on whether the individual has the disease. Okay?

Now superimposed on this is what we call the treatment model, which is to say what effect does treatment then have on these transitions?

In the case of Alzheimer's disease, we assumed as I pointed out earlier that disease is affected by

treatment in that it delays the likelihood of transition from year to year, and that's fairly consistent with the evidence in the clinical studies. So if you didn't get it the first time, I made another slide, and this is one of the dangers of putting me on an airplane is I make animated slides. The individual that we're talking about the scenario we called scenario A, patient starts with mild dementia in the first year. In the second year they continue to have mild dementia, but in the third year

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they progress to moderate and then in the fourth year they die. Okay? So that would be a sample patient history, and you can repeat this using this model any number of times you like and you can -- that's one of the reasons we call it, or I use the expression a trial in a box, is that you can create any number of synthetic patients using the strategy and as long as the underlying estimates are legitimate, then the projections should be reasonably legitimate. And I will point out that we did go through a process of validation to show that the model does in fact project natural histories that are very similar to the natural histories represented in the epidemiologic studies. So, the results. Here's the simplest way of representing the results simply in terms of true positive, false positive, true negative, false negative and total correct diagnoses. Again, pointing out that this is not the ultimate outcome, this is an intermediate outcome. What was see in the top row for the treat all strategy, everybody who gets treated, that is they're all treated as though they have disease, okay, and 55 percent of them, which is what we assume

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to be the prior probability of having disease, that proportion of people are going to be true positives. But also since everybody is getting treated as though they have disease, 44 percent of those people are

going to be false positives and therefore receive unnecessary treatment with whatever downside is associated with that. So the overall correct diagnosis rate for the treat all strategy would be 56 percent.
On the other hand, if we look at the test strategy, the test strategy actually has a significantly better correct diagnosis rate, which is 87 percent, because it more correctly partitions the patients without disease into the true negative category. You have 38 percent of people who would otherwise have been called positive under the treat all strategy are now being called no disease under the test strategy, so those people have now been able to avoid the use of treatment.
However, again, given the base case assumption which is that treatment is relatively benign, when that plays out in terms of looking at either quality adjusted life expectancy under what we call qualities, or simple life expectancy which is unadjusted for the quality of life, or the SDFLEs,

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which are the severe dementia free life expectancy, so that means basically on average, how long does somebody live without having severe dementia, so that's something a mildly demented person presumably would care about.
But by whatever measure, the treat all strategy turns out to be optimal, superior to both testing or to leaving the patient entirely alone. So just treating individuals who present with mild dementia after clinical evaluation without further testing is the optimal strategy.
Now, we were asked what if the test were perfect, and it's interesting to notice because of the way this whole analysis is constructed, namely that the clinical diagnosis actually establishes the presentation or absence of disease that even if the test were perfect, it could never be better than the clinical evaluation as long as the treatment has no downsides. That's really crucial.
However, once treatment starts to have a

downside, that's when testing becomes potentially useful. So you see all the way on the right in the upper right-hand corner, we see that when complications have no dysutility, they don't cause any significant decrement in quality of life other

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than the fact that the patient stopped the drug, that under that circumstance both treating empirically and testing have absolutely the same result because there is nothing subtracted for the fact that the patient has a false positive.
However, if a false positive starts to become worse and worse so you're going to the left, what's when you start to see some separation of the lines such that PET scanning becomes superior as the severity of the complications for drug treatment get worse. But I put in here that arrow there showing ten days. At the point at which the relative benefit of testing is at its maximum, the benefit is ten quality of life days, so that's a very very modest benefit under that circumstance, and that would mean that the complication would be equivalent in effect to saying that the patient experiences a decrement in quality of life of about a third of their full life quality. That's very severe decrement in quality of life.
Typically complications from drug treatment are modest and on the order of .95, .98, something that's as low as .6 is quite extreme, and one would suggest that when you start to get into that territory of dysutilities in that territory,

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people wouldn't even want to think about using the drug because it would be so onerous to think about a drug even if it only had a 10 percent likelihood of having a complication that bad.
So it's clear then that one of the big issues in terms of the value of testing is the value of testing in the context of a treatment not that's benign but a treatment that's not benign. And of course if the treatment were not benign, it would

have to be better than current treatment; otherwise, why would you be bothering with it. So, what we did was what we called a two-way sensitivity analysis or a threshold analysis if you will, and what this says is that on this figure, that plane there where all those little hatch marks are is all the possible combinations of drug complication severities. So as you go down the drug, if it has a complication that's a really bad complication, and as you go to the left, that if the drug is very efficacious, so all the way at the left basically, it stops the disease in its tracks; if it's at zero, that means it stops the disease in its tracks. So in the upper left-hand corner, it means it's a completely benign treatment, okay, and it stops the disease in its tracks, and under that

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circumstance you would clearly want to treat everybody without any further testing. On the bottom right, that would be a treatment that is extremely, or is completely inefficacious, has no effect on the progression, and further, that if they do have complications in treatment, it is equally inefficacious and you would leave that patient alone, you wouldn't want to mess with anything, under any circumstance. And then in that gray zone, intermediate territory are these combinations of these characteristics for which testing would be preferred. Well, we also -- so the results for the mild cognitive impairment patients would be that in a fairly robust fashion we conclude that for mildly cognitively impaired patients, treating all is a preferred strategy. So just moving on to the mildly cognitively impaired, not wanting to take too much time and since the results are almost exactly the same I will just point out that for the mild cognitive impairment patients, if we assume that medication effectiveness can be extrapolated to this population, and again, there is no evidence that mild cognitively impaired patients achieve a benefit from cholinesterase inhibitors, then treating all is the

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preferred strategy, or treatment after clinical evaluation without further testing is the preferred strategy. And again, this is a very robust conclusion.

So I'm going to move on to what I think is potentially one of the more interesting future possibilities for testing, which would be the use of testing in asymptomatic individuals, and this is a circumstance in which people are currently not being treated, even if they have a first degree relative, although there may be circumstance where people are being treated with the proper genotype plus a family history, whatever, but for the most part that's not happening. And the question might be in an asymptomatic patient if you could extrapolate the reduction in progression of disease to that population, would it be worthwhile to test.

So the base case results again, are very similar. It actually turns out that the lifetime probability of developing Alzheimer's disease among individuals with first degree relatives is quite high. That's assuming that they don't die of something else. It doesn't mean that 50 percent of them will get Alzheimer's disease, it just means if they don't die of anything else, 50 percent of them

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will have Alzheimer's disease by the time they are 90, I think is the number.

So we see again that the number of correct diagnosis is at the maximum for the test strategy but the true positives are at a maximum for the treat all strategy. Now again, what does that mean if we play it out with our clinical study in a box and do all the associated calculations? That the treat all strategy is again the preferred strategy. Why? The reason, again, is that we would assume that the treatment works, the base case is that the treatment has negligible side effects or negligible other than the individual has to stop the drug, and under that circumstance basically if it works, everybody should

get it. We're not talking about money now, we're not talking about any other consideration, we're talking about improvement in cognitive function or net cognitive function and we're talking about survival. And on that basis, the best thing to do if it works, if the treatment works is to treat everybody. Again, if the test were perfect, we see the same situation applies as before for the mild cognitive impaired patient, namely that when the disease, excuse me, when the treatment has effectively no severe complications, doesn't have any

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dysutility then at best, a perfect test will be identical to empirical treatment. But once you have a treatment that has a downside, then the testing strategy becomes preferred, and I put again this arrow, it's the same, I made this the same scale, so you could get a sense relative to the other scale that it's a fairly small preference, even under the circumstance where there is this fairly severe complication. So you're talking about a healthy person who is going to experience a complication that, can anyone help me here with a good complication that has a dysutility of .6, something like nausea? No, not nausea, maybe that's not a good one.

DR. ALBERT: Agranulocytosis.

DR. MATCHAR: Agranulocytosis, that's a good one, they survive it, but their white cells are wiped out temporarily, that would be pretty bad. So if there was a 10 percent likelihood of something like that, that was reversible by the way, would you be willing to put asymptomatic people on it. One might suggest not, but if you were, then the testing could be made preferred. And again, we did the same kind of two-way analysis with exactly the same conclusions with the asymptomatic population, is that

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we start with the base case where the treatment has no, is just fine, no big deal in terms of complications. It reduces the progression rate, I

didn't mention this before, but by about a third, progression rates. Others have estimated a higher decrease in progression rate but it really doesn't matter for the analysis.
As you go down the treatment gets worse, and you go left the treatment becomes more efficacious. And you see what's interesting is that if you do in fact have a treatment that's more efficacious in the future, then basically treating all becomes even more preferred. And if the complications become much more severe with treatment then the efficacy has to be concomitantly also much much higher in order for it to counterbalance the downside of the treatment.
So it's not enough that the treatment be bad, but that the treatment be more efficacious -- excuse me, that the treatment be worse, but also that the efficacy has to be a lot better. So there's no way to say in advance that a certain treatment is going to necessarily be preferred; you have to actually look at what its downside is and what its relative efficacy is. But now, given that this model

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is in your hands, you can use it for whatever purpose you want, should new evidence become available.
So let me just summarize. The conclusions of the analysis, that namely for patients with dementia who have had the recommended clinical evaluation, treatment without further testing is superior to treating based on PET, since treatment for this clinical scenario has been shown to be moderately effective and relatively benign. The increase in true negatives resulting from the use of PET is overshadowed by the concomitant decrease in true positives, so people who should be treated are going to not be treated if we actually take the PET result seriously.
For patients with mild cognitive impairment, if the evidence for treatment efficacy of cholinesterase inhibitors in patients with dementia can be extrapolated to this population of the mild cognitively impaired, then empiric treatment would

also be superior to treating based on testing. If the evidence for treatment efficacy can be extrapolate to patients who are asymptomatic but have an elevated risk of having AD by virtue of a first degree relative, then empiric treatment would be superior to treating based on testing.

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So, summaries one, two and three, no surprise, they are all the same. It's not a typo. And then summary, the fourth point is that PET scanning could be of value if a new treatment were to be developed that were more effective but had a risk of one or more of a variety of highly negative consequences. And I didn't go into this analysis, it's in the technical report, that there are many different ways that treatments can be bad. They can reduce quality of life, they can induce a progression of disease conceivably so that if a person does have a complication, it's possible there would be a treatment in the future that actually hastens the progression of disease, or it may cause death. So under that circumstance, PET scanning could become a strategy that would be preferred.

And I want to just make one comment to close, namely that there may be other reasons for testing that are not engendered by this analysis but also I should point out are not to our knowledge proven or demonstrated in clinical studies, namely that testing may conceivably improve patient planning, end of life planning, decision making about reproduction if it was a young individual who was a first degree relative, they may choose to change

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their decision to have children based on a PET scan result. It's possible that based on a PET scan result an individual might choose to be more compliant with drug treatment, simply having that physical test in front of him that says, you know, you have this disease, take your drug. And also, it may be that, and this is possibly related, that if testing is shown to predict responsiveness to

treatment, that could also improve compliance. But on the other hand, there may be other reasons for not testing. There is some suggestion that people who are asymptomatic who are labeled as having disease may have significant reduction in their quality of life and in fact may become quite depressed. And also being labeled may also interfere with employment and insurability, so there are those downsides to consider not explicitly included in the analysis.
Thank you.
MS. ANDERSON: Thank you. We are moving along so briskly that we have concluded that the break really isn't that important right now. We are going to take a very brief few minutes --
DR. PAPATHEOFANIS: Let's take a few minutes though, since we are moving along so briskly,

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and see if any of the panel members have questions for Dr. Matchar. Are we going to take a five-minute break then?
MS. ANDERSON: We're going to take about three minutes. I don't know if anyone wants to actually leave the room, but we just have to set up for our scheduled speakers.
DR. PAPATHEOFANIS: Are there any questions from panel members? Dr. Albert.
DR. ALBERT: I had a question about the prior probabilities you used for the base case results, and I was surprised that you were saying that the prior probability of having the disease in general was about 56 percent. I would have thought it would be higher.
DR. MATCHAR: You're talking about among individuals who --
DR. ALBERT: Among anybody.
DR. MATCHAR: Well, we used 56 percent. First, let me preface it by saying the exact number doesn't matter as long as it's somewhere in -- I mean, we used numbers that were somewhere in the middle range of 50 percent of so. That particular number came from a publication that I think

Dr. Neumann was involved in which was based on the

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results from the Harvard Alzheimer's clinic, and it was the proportion of individuals who ultimately had the diagnosis of Alzheimer's disease. In terms of the diagnosis of the asymptomatics, that was derived from an analysis of an epidemiologic study in which they statistically ferreted out what proportion of individuals would develop disease if you were able to turn off all other forms of mortality, all other causes of death. So it didn't mean that 50 percent of people were going to have Alzheimer's disease, but rather that 50 percent of people would develop Alzheimer's disease if they wouldn't die of anything else, but maybe just died at 90. It was a formal analysis that attained that. But all the probabilities are quite high, that individuals in these categories are all quite likely to have Alzheimer's disease. And if you made the probability higher, then you would actually strengthen the conclusion of the analysis.

DR. ALBERT: I would have thought that the probability was higher, particularly among very elderly individuals. That's why I was surprised.

DR. PAPATHEOFANIS: Sally.

MS. HART: What data or evidence did you

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have to assume that individuals would be willing to undergo treatment if there is no diagnosis that would support that treatment?

DR. MATCHAR: Sorry, say that again.

MS. HART: Your assumption that everyone will accept treatment in the absence of a test showing that there is a diagnosis that would support that treatment was somewhat surprising to me, and I wonder what empirical evidence you have that individuals would be willing to accept treatment without a test showing that they need it.

DR. MATCHAR: The analysis really didn't depend on that per se. I mean, it was saying for

individuals who would take the treatment if it were made available to them, but your point is well taken, which is that we're presuming that people on the basis of being told that they are likely to benefit from this treatment and that the treatment was benign, would take the treatment. There is no published evidence we drew on, but only the experience of the experts which have told us that this in fact is what happens is that in the community individuals, for physicians who believe that these drugs are useful and they transmit to the patients that they are very likely to have Alzheimer's

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disease, and that treatment could be effective in delaying progression, patients accept the drug, they do, and to the extent they don't accept it, the reasons seem to be that physicians are not all that convinced that the drug is very effective or that patients are not very happy about paying for the drug out of pocket, which is quite expensive, but it hasn't to do with whether they do or don't believe that they have disease.

DR. PAPATHEOFANIS: Sean.

DR. TUNIS: So if I understood correctly, the gold standard for looking at sensitivity and specificity of PET was always the clinical diagnosis, or at least that seems to be the way the model was constructed. And I know that there have been some studies, particularly the recent ones that looked at the sensitivity and specificity of PET related to ultimately the biopsy proven diagnosis post-mortem. And in that data, is there any evidence that PET is in fact potentially more sensitive and specific than clinical diagnosis or if so, how would that affect your models?

DR. MATCHAR: Well, in the one study that I'm aware of with regard to the biopsy and autopsy results, that the sensitivity and specificity using

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that as a gold standard was comparable to the results and was within the sensitivity analysis range that we

used for this model. There is no structural reason why the model couldn't use a different definition of what constitutes a true positive or real disease. Again, it was simply that the only evidence we had in hand about the value of treatment was based on clinical diagnosis. This is an issue we debated long and hard about and actually did come up with an analytic strategy for figuring out well, what if there was a true diagnosis that you might not be able to get at, but there was a true diagnosis that was even better than the clinical evaluation, and that both the clinical evaluation and the PET scanning were being compared to, and you're using histology as being potentially that gold standard. It could be done, it's not that it can't be done, it's just that there was no evidence that allowed us to understand how knowing what their biopsy result would be would lead to any better treatment decision. And in fact, some of the experts suggested that individuals without Alzheimer's disease might also be achieving some benefit from the drug and therefore, this notion that it would only be people who were biopsy positive might not really be the ideal criteria for treatment

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decision making. So again, the best thing that we have are the clinical trials and the clinical trials used clinical diagnosis as the reference standard, not the gold standard but the reference standard, and what's what we used.

DR. NEUMANN: Just to clarify on the assumptions on drug effect and duration, the base case assumption is 18 months of effect and the risk ratio is applied, the .72 through the 18 months and then goes away after 18 months, and no more effect is given.

DR. MATCHAR: That was again, the base case was sort of the standard conservative approach, which would suggest that you use the results from the clinical trials. The clinical trials were for something resembling that period, 18 months, so to suggest that drugs were going to be effective beyond 18 months would be going beyond where the evidence

takes us, or excuse me, would go beyond where the evidence is.
Again, in the sensitivity analysis we extended that assumption that treatment could continue indefinitely and also for the other scenarios given that we realized that the real potential was if the drug was going to be effective

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in the long-term, we allowed the drug to be effective in the long-term. So for asymptomatics, for example, patients continued on the drug until, or we assumed the patients would continue on the drug until they developed severe dementia.
DR. NEUMANN: And in terms of the assumptions on discontinuation or noncompliance, there is an assumption that some patients won't adhere to treatment, but there is no differential assumption that those patients will have a more severe decrement in utility, it's just that there's a general assumption about some percentage of patients who drop out or discontinue, is that how I understand that?
DR. MATCHAR: Right, that's correct.
DR. TUNIS: Just another question to clarify the model, and I think it came up in your second to last slide in terms of aspects of treatment or decision making that might occur based on a PET result that aren't formally incorporated in the model. So, the treatment intervention that the model looks at is only drug treatment or no treatment, so there's obviously many other aspects of management of patients with dementia or Alzheimer's disease that may or may not have quality of life benefit, and some

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of those are end of life planning, but others might be caregiver arrangements or other sorts of decisions about the management of the patient other than the drug therapy. And I'm just wondering whether your view is that that sort of is simply not modelable but we have to take it into account, or whether in fact there is no reason to take it into account in the

model because we don't know that those other interventions have effects on quality of life, et cetera.
DR. MATCHAR: I think reasonably that those things do have an effect on quality of life but that they are not going to be necessarily affected by whether one has the diagnosis of Alzheimer's disease or not. So that if an individual has cognitive impairment or functional impairment, that those interventions are generally aimed at dealing with the associated symptoms and with the burdens of the patient being in that state, not necessarily that is was because it was Alzheimer's disease. So those things would happen anyway, and should happen anyway. But I think in the asymptomatic situation or the very mild disease situation where there is just a very mild cognitive impairment, that would sort of fall into this notion of planning in that you could plan

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more in advance, that well, it looks like a few years from now we're going to need to really get into some kind of a living arrangement that's going to allow for a nursing facility if that becomes necessary in the future. So you know, being able to plan that way could be useful for the asymptomatic or the mildly impaired.
And is it modelable, that was the other question. Everything is modelable, there is nothing you can't model. And in fact in the context of this, if there was really a compelling reason to include it, we could do that, that's not a technically difficult thing to do.
MS. ANDERSON: Are there any final questions from the panel?
Okay. I am going to revise my original statement. We are going to take more than a few minutes. We're going to break down these lights and the video cameras, get everybody comfortable, so go ahead, leave, get something to eat, take a little potty break. We're going to come back in 15 and start up with the scheduled public comments.
(Recess from 9:54 to 10:20 a.m.)

MS. ANDERSON: Our first scheduled speaker Dan Silverman from UCLA, and he will speak to us

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regarding PET.
DR. SILVERMAN: Thanks, Janet: I was told that we could have the lights a little dimmer, since this is going to be image heavy material. In the next 19-and-a-half minutes, I want to spend some time in the first couple minutes to talk about some of the basic biology of Alzheimer's disease and the processes that occur, then what PET is actually capable of imaging, and then to overlap that, so we can see why what is actually happening in the brain that relates to other disease can be seen with PET and then move to what is I think more substantively important for the purpose of this session, which is to how that translates into the empirical evidence of PET's accuracy in being able to defect whether or not Alzheimer's disease and other dementias are present in the brain, and then finally turn to how the levels of accuracy that are obtainable translate into impact on clinical outcome.
So to begin, as is well known in histopathologic circles, there are two major hallmarks that are commonly cited for Alzheimer's disease. One is the neurofibrillary tangles which is the intercellular portion, and it's made of abnormal proteins called TAL proteins that have aggregated

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together because of problems in their phosphorylation unfolding, and this is shown more graphically here on a silver stain, the neurofibrillary tangles.
And the other are senile plaques which you see here on a silver stain again, which are an extracellular hallmark but again are caused by an aggregation of proteins, this kind of classic protein is called beta amyloid. And as you see here, this is something that has been in development as a PET probe that goes in higher concentrations to places where there are neurofibrillary tangles and senile plaques, and you see them lighting up very intensely in

fluorescence on both plaques and tangles. And what you see on the right is a brain slice, and it's stained specifically for the proteins, the beta amyloid and the TAL protein, and where it's darker, that means there's more of it. So you see around the cortex that there's high concentrations of those, and then you see with the probe, the bright fluorescence in the Alzheimer's brain, lighting up around those areas. And then you see in the normal brain the much lower binding of those probes around the normal brain.
And this is a PET probe that's currently in development, but of course FDG is a PET probe that

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is in common use clinically already for a number of purposes and the relationship between that and this is as you will see in many slides to come, where there's higher concentrations as lit up by this probe of the senile plaques and tangles, there is lower concentrations of the FDG, because those areas become less metabolically active because that tissue is less functional.
And FDG by the way is exactly the same molecule as the sugar that the brain uses for almost all its energy, which is glucose, except that this one oxygen-hydrogen, hydroxyl group has been replaced by a radioactive fluorine so it can be seen by the PET scanner. And so, although maybe the instrumentation of PET is a little complex, the biological principle is very simple. We're just mapping the glucose distribution in the brain.
And so, the question is why is such a simple biological principle so useful in being able to detect dementia like Alzheimer's disease and other neurodegenerative diseases and a host of other neurologic and psychiatric processes. And it turns out to be a very lucky coincidence of two things.
The first aspect of the lucky coincidence is that it turns out that the single most energy expensive thing

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that the brain does is synaptic firing, the

transmission of information from one neuron to the next and the restoration of the ionic radius needed to make that happen again.
And the second part of the coincidence is that almost exclusively, the fuel that the brain does to meet this energy need, that it uses, is glucose, and under starvation conditions ketone bodies. But it uses glucose and it uses glucose in an insulin independent way. So simply by mapping the distribution of glucose in the brain you have a very good map of the relative activity in the different parts of the brain. And most neurologic and psychiatric diseases that are advanced enough that they actually have detectable symptoms clinically have already involved enough brain tissue that is becoming dysfunctional that the normal very high level of metabolism in the brain becomes reduced in the areas that are involved, and that shows up as decreased metabolism as decreased uptake of the tracer, as less bright spots essentially on the PET scanner.
And this is an example of that. This is a normal brain for reference, showing the uptake of the glucose throughout the brain. This is a rainbow

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scale so just like in a rainbow where red is the highest part of the rainbow, red is the highest level of metabolism, and then orange, yellow, green, blue is the lowest level of metabolism here, blue and indigo. And what you see is that there is a high level of metabolism throughout the cortex, in fact it's a level that's six to eight times higher than occurs in the average concentration through the body of metabolism, and about half of that in the parts called white matter that are just below that.
And what you find in a patient with Alzheimer's disease is that the back portions of the brain, the parietal, the temporal cortex, the posterior singular cortex become disproportionately affected and become less metabolically active because they are becoming more involved by the pathologic process at a time in the early stages at least that

the frontal portions of the brain are relatively well preserved, compared to a frontal temporal dementia like Pick's where the frontal portions of the brain are decreased in metabolism at a time that the back portions are relatively well preserved; and Huntington's disease which has a pattern that's virtually pathopneumonic, you see this area that's normally the brightest part of the brain, the basal

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ganglia become almost ametabolic in both eventually the caudate nucleus and the lympha nucleus at a time when the cortex is relatively well preserved; and multiple infarct dementia is the one type of pattern on here that actually is more sensitively picked up by things like MRI and CT than by PET. And so, it's easy to know if that's what you have because if you see a defect like this and you wonder if it's a stroke, you just look on the MRI and if you don't see a core spine defect on the MRI, you know that's not what it was due to. Also within an individual, there is a close correspondence between the severity of the disease and what the PET scan will look like. So again, here is a normal for reference, and here's somebody in the early stage of Alzheimer's, this is someone who would just meet the diagnostic criteria and already you can see very easily parietal and temporal hypometabolism where it's much lower uptake here than the front portions of the brain. By two years later, which would correspond on average to about a 5-five point drop on a mini-mental state exam with 30 points as a perfect score, you can see that there's an advancement of the pattern so that this area that was hypometabolic in

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the back before in the temporal lobe is now also affecting part of the frontal cortex, including the prefrontal cortex that previously was well preserved. And by another couple years later, there's a decimation of almost all the associated cortex and most of the prefrontal cortex with just preservation

of structures that are mostly involved in sensation and motor activity, like the sensory motor cortex and the visual cortex and the basal ganglia. If we were on a lower plain you would see cerebellum and then the thalamus, which is the relay center for all that. And this in fact is very close to the pattern that you see on a newborn baby, who is after all born with all the facility to sense things and move around, but hasn't yet built up the memories and the cognitive complexities that fill the associative cortex and the prefrontal cortex respectively with metabolic demand. So this is kind of a neurologic substrate for what we often call a second childhood in these patients.

So, let's get to the bottom line. How sensitive and specific is PET in detecting neurodegenerative disease in general and how sensitive and specific is it in detecting Alzheimer's disease specifically. And this is a slide taken from

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the largest study to look at the sensitivity and specificity of PET against the gold standard of histopathologic diagnosis. There were 284 patients in that study, and half of them were followed longitudinally for a number of years after PET; the other half, definitive diagnosis was made by autopsy and I will show you just the autopsy results first. In this study of 120 patients who had neurodegenerative disease, PET said that they had neurodegenerative disease 113 of the 120 times, for a sensitivity of 94 percent. And of those who had no neurodegenerative disease, PET said they didn't three-fourths of the time for a specificity of that, and an overall accuracy of about 90 percent. Then if we ask the more difficult question, not only is there neurodegenerative disease here, but specifically is it Alzheimer's disease, you see again, of the 97 patients who had autopsy confirmed Alzheimer's disease, PET said specifically they had Alzheimer's disease 91 of 97 times, so again for a sensitivity of 94 percent, again a specificity among the 41 who didn't have Alzheimer's disease of

about three-fourths, and again, an overall accuracy of about 90 percent.
Then we asked the question beyond what the

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specific diagnosis that's is causing the dementia symptoms, what prognostic value does have PET have for predicting what will happen to the patients in the years after the PET. And for these purposes we defined three types of patterns as indicating a progressive dementia is present, one the type you saw for Alzheimer's disease where you have this parietal and/or temporal hypometabolism at a time that there's good preservation in other parts of the brain. A frontal temporal predominant patter, as you saw in the Pick's disease case for example, where there's relatively decreased metabolism in the frontal lobes and the anterior temporal lobes at a time there's better preservation of other parts of the brain. And the ametabolism of the basal ganglia that we saw before is virtually pathopneumonic for Huntington's disease. And everything else we called a non progressive pattern, which included normal of course, and included global metabolism; this is hypometabolism that's due to just less tissue being there because of atrophy, as opposed to less metabolism per gram of tissue that's remaining. And then other focal defects that didn't correspond to the previous slide, the most common of course which would be strokes that cause focal areas of

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hypometabolism, and as you can see here on this MRI, are much easier to detect on structural imaging than on functional imaging.
So what we found is that when we looked at the patients who had positive PET scans, that is positive for progressive disease, that in fact just within a year and a half after the time of the PET, there was already a significant decline in the MMSC, and remember a perfect score would be 30, and by another couple years there is another significant decline in the score, as opposed to the patients in

whom PET found a nonprogressive pattern, and which you can see that even out to three-and-a-half, four-and-a-half years later, although there was a trend toward some decline, there was no significant change in MMSC score over that same period of time. And you might say well, maybe it's because these patients are starting off a little better functioning than these patients were to begin with, so we also looked just exclusively at the patients who were very level high functioning to begin with, that is, those who had an MMSC score of at least 26 on a 30-point scale, and followed them out over the period of time of five years. And again in red you see those who had a progressive pattern on the PET,

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and some of these patients fell from as high as 26 to 30 to as low as 5 over this five-year period. And yet, not a single patient who had a nonprogressive pattern fell to lower than 25 from their initial 26 to 30 over that same five-year period. We subsequently confirmed this with a larger group of patients, and the statistics only became stronger. And so putting these two parts together, asking what is the prognostic value of predicting progressive dementia, either because progressive dementia is found by actually watching the patient's dementia progress, or because they had an autopsy that identified whether or not a progressive dementia process was present in the brain, of the 206 patients who had a progressive dementia as documented in one of those two ways, PET specifically said they did have a progressive dementia 191 of those 206 times, for as sensitivity of 93 percent, and again a specificity of about three-fourths and again, an overall accuracy of about 90 percent. So both in terms of diagnosis and prognosis, PET had high sensitivity and reasonably high overall accuracy in predicting whether Alzheimer's disease was present and predicting whether there was a progressive dementia present in

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general.
We also looked at this in comparison to doing clinical workup without the benefit of PET and we asked neurologists at the time that the patients were referred for PET, did the patients have or not have a progressive dementia. In about one-third of the cases the answer was that that was indeterminate, they couldn't tell either because the presentation clinically was too atypical or the differential diagnosis was too wide. But even if you look at just the two-thirds for whom they thought they knew the answer, if they said a progressive dementia was present, 78 percent of the time they were right; and if they said there was no progressive disease, 27 percent of the time they progressed anyway, for a relative risk of 2.86, ignoring the ones who they thought they didn't know the answer to.
If we compare that to the patterns demonstrated on PET, what we find is that of those who PET had a progressive pattern, 81 percent actually progressed. Of those who had a nonprogressive pattern, only 13 percent progressed, for a relative risk factor of 6.22. So just PET by itself being used at this point in the algorithm had a two to three times higher predictive power than all

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the other information available to the neurologist up until the time that PET was performed.
Now, I'm going to turn to how does the sensitivity and specificity as defined in this and other studies translate into impact on the management of dementia. And to begin with, it will be necessary to talk a little bit about how the normal process of clinical diagnosis is done without PET and how it's done with PET according to the recommendations and according to the criteria in the coverage request to Medicare, and this is a little more than fits on one slide, so someone is going to help me when we get to the bottom, but in the conventional evaluation what happens is as in most neurological psychiatric diseases, patients get a good history and physical exam as they would with PET, and they establish

whether or not a cognitive deficit is actually present that represents a change from the patient's baseline. If that is the case, then it's determined whether or not they meet the criteria for dementia by having multiple cognitive domains present and functional decline present and if so, then a number of things are tried to be ruled out by history and physical and a panel of relatively cheap and easy to obtain common labs.

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And if all those are negative, then the diagnosis of AD is clinically made. If some of those are positive, then treatment is obtained and then the patient is reevaluated and if they don't meet the criteria of the dementia like MCI patients, then it's recommended, and this is the American Academy of Neurology recommendations by the way, that then they get reassessed, typically six months to 12 months later and then see whether or not they meet the criteria for dementia and whether anything else has arisen that would need to be treated for in order to exclude other diseases.

If there are specific neurological symptoms present, then there is a number of specialized neurological tests that can be done, and just this year the American Academy of Neurology revised their recommendations to suggest that virtually everybody who gets to this point in the evaluation should get a CT or MRI done in the process of excluding other diseases.

This is the algorithm for incorporating PET into the evaluation and it starts off much the same, comprehensive history and physical and documenting whether or not a cognitive deficit is present and if so, are there any specialized

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neurological things that require specialized tests, and this is all done identically and all modeled exactly the same in both studies. And then regardless of whether they meet the criteria for dementia, so this looks basically at patients who

have MCI and dementia together, the question is, are there any conditions from the history and physical, common labs, that could be giving rise to their dementing symptoms and if the answer is yes, then again, they should be treated. And if the treatment completely reverses those symptoms of the cognitive deficit then there is no need to go further, there's no dementia to diagnose or disease to diagnose at that point, but if they still have a persistent deficit then those patients would be considered an appropriate candidate for PET scanning. Likewise, if they have this cognitive deficit demonstrated and there's no other conditions that could be causing it that are identified in the history, physical and common labs, then in that case those patients are considered appropriate candidates for PET. So the bottom line there is that basically patients either have to have a positive diagnosis made and there has to be a reversal of symptoms if they're diagnosed with something other than

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Alzheimer's disease, or else those patients would be considered to be reasonable candidates for PET. So we modeled this explicitly in an algorithm that as in the case of a technology assessment would be far too cumbersome to go into detail in the time we have here, but it's a decision tree analysis as done in the technology assessment looking at the PET incorporated pathway versus the non-PET incorporated pathway and coming up with impacts on clinical outcomes as I will discuss now. So the input going into this was what is the sensitivity and specificity of PET, what is the sensitivity and specificity of clinical evaluation, and what you see here is that this is the clinical evaluation's accuracy as assessed by the American Academy of Neurology. They identified a total of three studies that they considered were class one studies, that is, had high quality of evidence, and only one of those focused on patients in early stage of disease, as both the technology assessment and we have focused, patients who have MCI or patients who

have mild to moderate Alzheimer's. And that study showed that there was a sensitivity of 83 percent and a specificity of 55 percent if they used probable AD criteria as recommended by the American Academy of

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Neurology, and otherwise if they used possible plus probable, a slight difference in those. So we took an average between those two since the difference was slight, and some people do actually get diagnosed on this basis in the evaluation that you're going to see.

And in the other studies, the sensitivity was much lower with probable AD as a criterion, and it could be increased by adding the possible AD but at the price of specificity, to substantially lower than PET. This is the study that I just talked about with the 94 percent sensitivity and 73 percent specificity, and you can see that's very close to the range of the other studies that have been reported in the literature where PET accuracy was measured against the gold standard of histopathology diagnosis.

And to sum those up, if you use the clinical evaluation of probable AD, the sensitivity ranges from 17 percent below to 17 percent above 66 percent, the specificity is 77 percent, and the clinical evaluation of probable plus possible, the sensitivity comes up to about the same level that it is in PET, this is taking the average of all those three studies that I showed you on the previous

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slide, but at the cost of the specificity which now is substantially below that of PET. And if you look at the overall accuracy impact on average prevalence populations, the technology assessment said 56 percent and we said 51.6 six percent, so the same ball park. Then the accuracy for the PET in this population turns out to be 85 percent by this assessment and the overall accuracy for conventional is 69 percent. In the technology assessment they estimated their overall accuracy as to the

prevalence, which was 56 percent in the case of dementia, which was 80 percent in the case of the MCI, and so if you take a halfway point between there, it would be 68 percent overall accuracy. So what this translates into in terms of number of false negatives and false positives is that in the conventional algorithm, a false negative rate of 8 percent and in the proposed algorithm about 3 percent, a false positive rate of 23 percent versus 12 percent, and so overall a false diagnosis of 31 percent versus 15 percent. And if you measure what that means for 100,000 patients that are evaluated and then clinical impact, for a false negative diagnosis of 100,000 would be, that are fewer by using PET than by not using PET would be about 5,000,

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and false positive diagnoses fewer by using PET would be about 11,000. And in terms of what that translates into for final clinical output, with PET that corresponds to between 45,000 and 91,000 fewer months of nursing home care needed, and in the case of the false positive diagnosis that are reduced, about 131,000 months of unnecessary drug use the patients are saved from. And how does that compare, finally, with what was projected in the clinical algorithm? Well there the overall accuracy that they deduced for PET turned out to be very close to what we deduced, 87.5 percent, which they got by a sensitivity that they assume was a little bit lower and a specificity they assumed was a bit higher, and I can talk if there is more time in questions about the exact differences between those and why those arose. And what that means in terms of false positives and false negatives are shown here. There's still a few more false negatives percentage wise, a fewer false positives percentage wise than was predicted, and the total false diagnosis rate they got by this would actually be a little bit less by their projections of PET's accuracy than by our own projections of PET's accuracy.

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And finally, what that means in terms of clinical outcome can't be predicted exactly with the technology assessment because they made the assumption as was discussed that they didn't specify a sensitivity and specificity, that's why there is nothing shown here. What they did instead is just made the assumption that basically the sensitivity was being operationally set to 100 percent, specificity was being operationally set to 0 percent. But if you use the same clinical data that the American Academy of Neurology has give for that, then these would be the numbers that would apply and again, there would be in this case about 20,000 months of nursing home saved by using PET versus the clinical algorithm, and about 200,000 months of unnecessary drug use that would be saved by using PET in the clinical algorithm.
So in conclusion then, we have going back to the beginning, changes in the brain that occur in the course of Alzheimer's disease that occur early relative to the time that symptoms manifest. In the TEC assessment they cited literature that shows at least ten years early. And those are changes that are easy to detect by PET so that diagnosis can be made sensitively at an early stage of disease and

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that translates in terms of clinical outcome into many months of unnecessary nursing home care that are saved and many months of unnecessary drug use that are saved.
I'm out of time, a little bit past, so thank you.
MS. ANDERSON: Actually, if you'd stay for a second, Dr. Silverman, we're going to allow the panel to address any questions that they might have at this time.
DR. SILVERMAN: Sure.
DR. McNEIL: I have one question, and your images were really quite lovely, but here's the question regarding the first part of your presentation. The voting question that we have says,

is the evidence adequate to demonstrate that PET has clinical benefit in evaluating patients with suspected AD? Could you say a little bit about how the first half of your presentation addresses this question?
DR. SILVERMAN: Yes. The panel assigned the technology assessment to consider that question with respect to three sets of conditions, asymptomatic, MCI, and actual AD. So in the case of MCI and asymptomatic -- and we by the way are not

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arguing for use in asymptomatic patients, only for patients who would essentially be MCI or actually have early stages of dementia. It's important to see that there are changes going on in the brain that it's possible for PET to find, so noting that even if the patient hasn't yet met diagnostic criteria for Alzheimer's disease, that among those portions of MCI patients who will eventually develop Alzheimer's disease, those changes have already occurred in their brains and that those are changes that PET will be able to see in their brains, be able to sort out which of the patients who are coming in as MCI actually do have Alzheimer's in the incipient stage, versus which of the patients actually have other things that are accounting for their impaired cognition.
DR. McNEIL: It's a little confusing because the question implies that we are taking a cohort of patients that are patient at time one, at least that's how I read it, and what you're suggesting is that we should be looking forward and following patients, and then at some point make a judgment on the basis of cumulative evidence from many different sources over many many different years. And I'm just wondering if that's what we're

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supposed to be doing.
DR. SILVERMAN: Let me actually give a little bit different perspective on that. In the negative diagnostic sense, that's actually not really

what's happening, because what we're saying by a prognostic assessment, and I think that's what you're referring to, is that a patient doesn't have a progressive dementia, so those are patients who shouldn't be treated if you're going to treat patients based on what the diagnosis is.
DR. ALBERT: I have a question about the answer you just gave. Did you present any data about MCI just now? I didn't think that you did.
DR. SILVERMAN: Yeah, all this data applied to patients based on being in an early stage of cognitive decline regardless of whether by clinical evaluation that would lead the categorization as MCI versus, that may be on its way to AD, versus having actual mild AD.
DR. GUYTON: Then where did your number of 100,000 people evaluated come from, is that some number that are evaluated over a certain period of time?
DR. SILVERMAN: No, no, I'm just saying per 100,000 evaluated, that's a number just to give a

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rate so that I can get rid of decimal points basically. So I gave false positives, false negatives in percentages, which would be per 100, but those had numbers like 5.16, so in order to clear the decimal points I just said per 100,000.
DR. GUYTON: And how does that translate into 131,640 fewer months per year? I don't understand where those numbers relate.
DR. SILVERMAN: That's actually a very simple calculation, and that was supposed to say months of unnecessary drug use, so that's based on 11,000 fewer false positive diagnoses, and so if patients who have the diagnosis are being treated, that means there's an extra months per year, 130,000 patient months per year who are getting treatment that they don't need.
DR. GUYTON: How did you come up with the 130,000?
DR. SILVERMAN: Just 12 times 11,000, that's the number of months per year. So if this is

a false positive diagnosis rate, there are 11,000 fewer, which would correspond to a 130,000 fewer months per year of unnecessary drug treatment. I put it in terms of months because that's how the nursing home data is generated, so to make those comparable,

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but how long that goes depends on how many years those patients remain on therapy, which in many cases could be much more than one year.

DR. NEUMANN: You mentioned two outcomes that were not mentioned in the Matchar model that could be important here. One is months without drug use, and the other is months of nursing home care needed. I understand if you compare PET versus drug how you could get many fewer months without drug use by testing. What's not clear to me is how you get the fewer nursing homes, if you're comparing it to treating everybody for example, as in the Matchar model, and you assume that the drugs work, how do you get that conclusion?

DR. SILVERMAN: That's a very good point and the assumption here is that patients will be treated according to their diagnosis, whether that diagnosis is made without the use of PET or whether the diagnosis is made with the use of PET. And so the difference in the diagnosis of the rate of Alzheimer's disease is this difference of in this case 5,000 per 100,000 people evaluated, and then that translates directly into nursing home care by taking an abundance of literature on rivastagmine, anglatamine and epistagmine, showing that there is

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about a 9 to 12 month delay in the progression of symptoms. And in the case of the TEC assessment, they used I think an ultraconservative estimate of six months and if you use that then this would translate into 30 months of nursing home care that would be saved.

And the second part of your question is how does it compare to treating everybody. If you're treating everybody then that would not be the way

that you would make this comparison, but if you treat everybody, there's no point in doing a TEC assessment in a sense because it doesn't matter what the test is. Any test that doesn't label 100 percent of the patients as having the disease would come out with the same shortcoming.
DR. NEUMANN: Right. But to make an apples to apples comparison of your evaluation with the Matchar model, you would want to compare PET versus treating everybody and --
DR. SILVERMAN: Yeah, I would have loved to be able to make an apple to apple comparison by having them do their TEC assessment in the way that we generated these numbers. That's why I put these in parentheses, because they didn't do it that way. They already, you know, told you what the numbers

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would be if they did it their way, so I was trying to show what the numbers would be if they did their analysis our way.
DR. BURCHEIL: I'm still confused about the nursing home question, and maybe I'm just missing something, but the nursing home consumption is based on a functional status, not on the basis of test positivity. I mean, I can understand treating all, or even treating a group with drug, but you're not going to hospitalize someone for a positive test; they are hospitalized or placed in long-term care based on their functional status.
DR. SILVERMAN: That's absolutely right. And so what the nursing home care is based on are patients who actually have Alzheimer's but then fail to get treated because they're not diagnosed with Alzheimer's, and so then they progress 9 to 12 months faster and so have that much more nursing home care needed, and that's done by progression data. There's also direct empirical data that have looked over the long term of the number of months of nursing home care that's actually saved in patients who get treated versus patients who don't get treated and those range from between 9 and 24 months.
DR. ALBERT: And what about the reverse,

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the people who are said not to have the disease on the basis of the test but do, and don't get treated?
DR. SILVERMAN: Yes, those would be patients who would have a false negative, and there would be more patients if you didn't insert PET into the algorithm who would be assigned a false negative diagnosis than if you did insert PET into the algorithm. So those patients are patients who are suffering the worst possible consequence, that is, there's a drug available for them, but they're not getting treated for, but without the insertion of PET, more patients would miss being diagnosed as Alzheimer's disease.
DR. McNEIL: I have one question. It's very hard, as you can imagine, to evaluate a model that's this complicated with a few slides, so here's my question. In maybe one sentence, could you tell me if you put in the treat all option in your model, if you had done your analysis with a treat all option and had excluded as an outcome nursing home days, would your results differ from any of the broad range of sensitivity numbers that the Duke model showed and if so, what would be the key component contributing to the differences in the sensitivity analysis in the broad range, not talking about point estimates, but

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within the sensitivity range?
DR. SILVERMAN: That question we can answer numerically here. And for PET, there is not any substantial difference in overall accuracy of PET based on --
DR. McNEIL: No, that's not my question. My question is, if you were to take your model and carry it out to impact on outcomes, quality adjusted life years, and put the treat all option as one of the original three decision nodes, would there be a difference?
DR. SILVERMAN: This model was actually not designed to query for quality adjusted life years because as was pointed out by Dr. Matchar, it's

unclear whether it's good to have people live longer in an advanced state of dementia. What we really want to do is keep people from being severely demented during the time that they're alive. So we made as our outcome measure there and as a proxy for that, the number of extra nursing home months that would be needed, as indicating the severe functional decline associated with the dementia.
DR. PAPATHEOFANIS: But she is asking you to hypothesize, let's say that you could do this, what would you predict, if any difference would occur

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in your model versus the Duke model.
DR. SILVERMAN: I think that there would not be much. I mean even in the Duke model what you saw was differences of about one to two one-hundredths of years between the two, and so whether you bring down the clinical a little bit or leave it where it was, it will just be a matter of whether it's one or two hundredths above or one or two hundredths below when using those measures.
DR. NEUMANN: We haven't done the analysis so we don't know exactly, but my strong guess, the answer to your question is nothing is going to change the base conclusion of the Matchar model. You might have a slightly different number on percent diagnosed correctly in your model, my guess is you will have a slightly different number. The other thing you have that the Matchar model does not have is this number of unnecessary months on drug treatment, and that's an addition to the model but doesn't change the basic conclusion of the model.
DR. SILVERMAN: No, as far as unnecessary months, I mean that's easily derivable from their model and they don't measure that because they assume it's unimportant. But as far as the thing that would really change the clinical outcome, you say nothing

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would much change in our model; nothing would much change in out model if you begin with the assumption that you treat every person regardless of what the

diagnosis is, as long as they are symptomatic either for dementia or symptomatic for MCI, which is what happens in their two trees. Now that's self evidence, but that's not what happens in real -- well, you'll hear Dr. Small talk more about what happens in real practice is that not every patient who comes through that has symptoms gets treated as if they have Alzheimer's disease, and it's not clear whether that should happen. There's a number of reasons why to suggest that that shouldn't happen. And as the panel raised in their questions during that time, it's unclear whether even if we thought that that should happen, whether you could get patients to buy into that and have them be treated in that way. But we can think of it in maybe concrete terms in that if -- you probably all have recognized some change in memory or language abilities in a father or mother or husband or wife, or maybe in ourselves, and if we to the doctor and said you know, I have some symptoms, and the doctor does the workup and says yep, you have those symptoms, let's start you on a drug in case it's

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Alzheimer's disease, compared to going through a diagnostic process that says yes, we can say with high likelihood that you do have or don't have Alzheimer's disease, the likelihood that you would get patients to be able to buy into those kind of treatments is probably going to be very individual and not going to be uniformly applied across the patient population.

MS. ANDERSON: Thank you, Dr. Silverman. And just one last thing which is, for the record I need you to declare whether or not you have any financial interest with the manufacturers of PET or with their competitors.

DR. SILVERMAN: I have no financial interest with any manufacturer of any instrumentation related to PET or any PET related pharmaceutical.

MS. ANDERSON: And your affiliation?

DR. SILVERMAN: With the University of California Los Angeles School of Medicine.

MS. ANDERSON: Thank you.
DR. PAPATHEOFANIS: There is one last question.
DR. TUNIS: I just wanted to clarify. So in the effectiveness of drug treatment that comes from the clinical trials, all those patients were

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enrolled in the trials based on the clinical diagnosis of suspected dementia, to be eligible for the drug trials. So now when you're looking at those who are, in modeling those who are confirmed to have Alzheimer's by PET, are you assuming then that the ones who were an errant clinical diagnosis would have in fact not benefitted from drug therapy? Is that a reasonable judgment or extrapolation from your trial data?
DR. SILVERMAN: No. Really the answer to that question is not known one way or the other. We are in the case of patients who have MCI, there are a number of patients who have some degree of cognitive impairment that has nothing to do with Alzheimer's or any other neurodegenerative disease and may even just be related to processes that don't need treatment at all. So we are assuming that in the patients in the MCI category that those who actually have Alzheimer's disease in their brain are more likely to benefit from the drug treatment than patients who don't actually have Alzheimer's disease in their brain.
DR. TUNIS: But the trials don't actually tell us that, because those trials are treating people, some of whom do and some of whom don't.
DR. SILVERMAN: That's right. So the data

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for that don't exist one way or the other, so the technology assessment made the other extreme assumption that because even despite that those numbers are not in, that every patient with MCI who gets treated will have an equal likelihood of actually responding to the drugs and will respond to the drugs, which that clearly is untrue, and the question is how untrue is the other assumption.

DR. PAPATHEOFANIS: Thank you.
DR. SMALL: Good morning. My name is Gary Small. I am a professor of psychiatry and aging at UCLA. I appreciate the opportunity to speak to the panel about this issue. I do not have any conflict of interest with the relevant companies in these discussions regarding imaging. I have been working in this field for about 20 years now taking care of patients with dementia and Alzheimer's disease, working with imaging probably more in the last 15 years, working in the research with PET and other imaging modalities, and also in the use of PET in my own clinical practice. So I'm going to present a clinical perspective augmenting some of the comments that Dr. Silverman just made.
Now we've heard some of these estimates that you see here. We know that dementia and

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Alzheimer's disease are age related illnesses; 5 to 10 percent in the 65 plus age group suffer from these conditions, about four million people in the U.S. The costs are quite high, and there are a number of different estimates about the costs. Unfortunately, many mild cases go unrecognized and as we have heard, most of the time dementia is from Alzheimer's disease, about two-thirds of the time.
In fact, if you look at studies like the one we see here, you have about 66 percent of patients with Alzheimer's disease, other progressive dementias are causing some of the dementia symptoms, and then we have potentially reversible causes in about, completely reversible causes about 5 percent of the time. With Alzheimer's disease we have a gradually progressive course and it starts out with very mild cognitive symptoms we've heard about, it affects the person's daily activities, their ADLs or activities of daily living become impaired, there are behavioral problems eventually, there's nursing home placement and death, and this can happen over the course of years. We receive the mini-mental state score versus number of years.
We have a lot of challenges with the

diagnosis and I thought it would be helpful to review

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a few points about the real world in terms of diagnosis. The first is that PCPs or primary care physicians are the ones who are caring for most of these patients; about 64 percent of dementia patients are cared for by the generalists. A study a few years ago found that unfortunately, these primary care physicians have limited knowledge of Alzheimer's disease and dementia. In fact, in Barrett, et al., in their study only 40 percent of the PCPs knew that Alzheimer's disease was the most common cause of late life memory loss compared with experts who knew or had about a 97 percent knowledge rate. Primary care physicians also usually do not use the standard diagnostic criteria to make their diagnosis that we have heard about from the American Academy of Neurology and other groups that have come up with the standard diagnostic methods.
Callahan and coworkers found that there is a very high rate of misdiagnosis with moderate dementia, it's about 75 percent in this particular study of several thousand patients. In mild dementia it can be as high as 97 percent. And with under-recognition we all know about some of the problems. We get higher hospitalization rates, ER visits, motor vehicle accidents, medication errors,

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morbidity and mortality.
We have heard about the current standard approach to diagnosis and assessment, I won't go over this in detail. I sat on the recent panel of the American Academy of Neurology looking at the diagnostic approach, and I will talk about that in just a moment. We have heard about the treatments, there are many potential treatments out there, but right now the standard of care is to use a cholinesterase inhibitor and vitamin E.
It's interesting when you look at this cartoon showing us some of the cholinergic projections that the basal forebrain has a

concentration of cells that produce acetylcholine. These cells project to the frontal cortex, parietal cortex, hippocampus or temporal regions, the areas that we see on the PET scan where there are decreases in function in Alzheimer's disease. These drugs as we have heard will not only improve memory and retention but they will delay decline, they delay nursing home admission, they also benefit behavior, the activities of daily living, and appear to improve caregiver burden or at least slow down the worsening of the caregiver burden.
Now this was a study that was published

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about a year or so ago, and it's one of the typical clinical trials that are done with these cholinesterase inhibitor drugs, and they're based on samples of hundreds of patients with Alzheimer's disease, mild to moderate severity in general, and what we see in the vertical axis is the change in the A-COG score, which is what is used to test these drugs, and here we have months of treatment. The drug being tested here was Galantimine and it was compared with a placebo group. And we see over the first six months that there is in general improvement in the active drug group in the double blind trial, and you can see the placebo group worsens over the six-month period. Now what's interesting about this study, and I have seen a similar study with rivastagmine, another cholinesterase inhibitor, what they decided to do in an open label fashion after six months was to put the patients in the placebo group on active drug, and you see there is improvement in that group, but that group never quite gets to this level of cognitive function that people who started out six months ago on active drug are at, and that difference continues to the 12-month period. Now there are methodologic issues such as dropouts and other issues about interpreting these kinds of data,

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but certainly it is interesting that there is this apparent loss of gain, or let me say it this way,

there is an apparent gain if you start patients earlier in their treatment, arguing for earlier detection or advantages for earlier detection. Another interesting observation. When you put patients on these drugs, I mentioned that there are behavioral benefits. We can see that in this analysis which we published a few years ago where when we compared a group of patients on active drug, and in this case it was Donepezil, versus a group that was not on the active drug, that you see the patients who were on the active cholinesterase inhibitor tend to use fewer antidepressants, antipsychotic medicines, antianxiety agents and sedative hypnotics. In fact, the differences were significant for most of these agents.
And just to show you some data on the effect on caregiver burden, this again was a six-month trial with Galantimine and the measure on the vertical axis has changed from baseline in daily time spent assisting with activities of daily living, and this is the actual time the caregiver spent each day. I think these are remarkable data because what you find over a six-month period, that patients on

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placebo, their caregivers are on average spending another 20 minutes per day on their patients. By contrast, the patients who are on active drug, there is a reduction of 40 minutes per day, so you're talking about a substantial amount of time, maybe an hour's time per day per caregiver, which really adds up.
One of the assumptions that we've heard about today is that these drugs are pretty benign, that they cause some temporary side effects, that people tolerate them well, and so we can possibly assume that there is no downside in taking a cholinesterase inhibitor. Well, I thought I would present a contrary point of view taken from the clinical trials to date, including data from the PDR and other clinical trials. This just gives you the most frequent side effects you see from cholinesterase inhibitors, generally GI side effects

such as nausea, vomiting, anorexia dyspepsia. You can also see bradycardia and in some cases some agitation. In the clinical trials that I reviewed here, nausea occurred in from 5 to 50 percent of patients, compared with the placebo group where you see it from 3 to 28 percent, and that's going to vary depending on which cholinesterase inhibitor you use,

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how aggressive you are in increasing the dose. It is true that these effects tend to improve with time and if you increase the drug gradually, you are going to get fewer of these side effects. However, you still have dropouts from these clinical trials due to these adverse events anywhere from 7 to 32 percent of the time, compared with placebo treatment arms where it's 1 to 8 percent.

There's an added value of early diagnosis. We've heard about some of these arguments before. We can identify candidates for treatment before there is extensive neuronal loss. Early on we're going to have the greatest impact. We heard about the argument that we don't want people to get to a severe dementia stage so if we can detect people earlier, we can treat them earlier and delay the onset of that severe dementia stage. There is a potential cost saying by avoiding years of multiple diagnostic evaluations and I will give you some examples from our own clinical case material about how that happens. And even if we didn't have effective treatments, there are many people, and I've seen it in my own clinical practice, who want to know about their prognosis while their mental faculties are intact so they can plan for the future.

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We saw from Dr. Silverman some of the benefits of PET in terms of the sensitivity and specificity. We know that Alzheimer's disease is prevalent, it can be treated, and we can treat it in the early stages. The current approach to the dementia diagnosis often involves multiple costly assessments performed over years. PET provides an

early differential diagnosis for Alzheimer's and other dementias. And in fact we can see this classic Alzheimer's PET pattern many times in patients even years before the diagnosis can be confirmed clinically.
This shows you one case of a patient, here's the MRI scan and the PET scan, and the MRI shows atrophy and some white matter changes, some periventricular capping, nonspecific findings that don't help you with a positive diagnosis of Alzheimer's. By contrast, the PET scan shows you this parietal temporal deficit which is diagnostic early on.
Now in the American Academy of Neurology practice guideline committee, we used an evidence based approach to the diagnosis and we had different classes of evidence, and if we look at class one studies that are relevant here, and the class one

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study would be defined as having prospective design, a broad spectrum of patients, gold standard for case definition and blinded evaluation, there was really only one study of standard clinical diagnostic methods used in the early detection of dementia that met these criteria, and that was a study that Lim and associates published a few years ago in the Journal of the American Geriatric Society.
There were two other studies that met class one definition of the standard diagnostic criteria but these were really studies of patients who were in the moderate to the more severe stages of dementia. In this study they actually spent several years in making their diagnosis. So what they found after several years of assessment and using as the outcome measure autopsy confirmation, diagnostic accuracy in the Lim study was in about the mid-80s and specificity was 50 to 55 percent.
By contrast, if we look at the study that Silverman and associates published just recently where we looked at a single baseline PET scan, and these are some of the data that Dr. Silverman just presented, in 284 patients, so we're looking at a

single baseline PET scan comparing another level one or class one study that had multiple assessments over

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several years, we see this higher sensitivity in the 90s and specificity in the 70s.
Now here are just a few examples from our case material in our memory clinic. This was a 73-year old widow who was brought in by her adult children after a year of symptoms of depression and forgetfulness after the husband's death. There had been a normal MRI scan except for some nonspecific atrophy, and the question I was faced with was whether to treat her with an antidepressant drug or to start a cholinesterase inhibitor. And being aware of some of the delayed start data I showed you earlier, that is, if I wait to start her cholinesterase inhibitor, if I spend months trying to adjust her antidepressant, I may lose ground, I may not get the best benefit. So we did a PET scan, a PET-FDG scan, and we saw parietal temporal deficit and started her on a cholinergic drug and in fact her cognitive symptoms not only improved but we saw some improvement in her depression as well.
Here's a second case of a woman who had multiple examinations by psychiatrists and by neurologists over about a two-and-a-half year period and serial MRI scans, and there were many different diagnoses including depression, attention deficit

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disorder, fibromyalgia and so forth, and the woman had really not gotten any definitive treatment. We did a PET scan and it showed this Alzheimer pattern. We started her on a cholinergic drug and we saw improvement within a matter of a few weeks.
When we looked at some of the initial cases in our memory clinic, and these are people who come in, the clinic tends to focus on people with milder memory complaints, and they have some concern about their cognitive complaints, and of the first 60 patients we thought that a PET scan would be useful in 38 percent of them, because of diagnostic

question. If a patient already has moderate dementia and it's pretty obvious what they have, we're not going to get a PET scan. In this series of patients we found that about half of them, 57 percent had essentially a normal scan. When we just looked at the MCI subjects, we found that about 50 percent had a normal scan; on the other hand, of the total, 43 percent of the patients had a pattern that was consistent with a neurodegenerative disorder. We have been doing research over a number of years focusing on this asymptomatic group, people who have no symptoms or else have mild symptoms, and may not get MCI or dementia for a number of years,

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maybe even decades. And we found that when we combine information about genetic risk such as the EPO-E4 alial that you can begin to see this Alzheimer's type pattern with the parietal deficit, the posterior singlet and temporal deficit in these people, and this is a very interesting area of research, and in fact we're doing some studies right now, clinical trials in people who have age associated memory impairment. But this is not something that we think is ready for general clinical use. We think we need to do the studies to show that it actually is effective in an asymptomatic person or not effective, before we can make that kind of recommendation.

Just to wrap it up with a few key points to summarize what I have said, first, the diagnosis of dementia is missed in a large proportion of patients. We saw the data from Callahan, et al., and there are other data confirming this. The current clinical approach to the dementia diagnosis is often inaccurate and it involves multiple examinations over the years. We saw that from our own individual clinical cases and we have seen that again and again from the different summary studies. Current treatments are effective, but they do have side

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effects, and this would raise questions about the

assumptions we've heard earlier that there is no downside in using a cholinesterase inhibitor drug. We've seen that PET adds to the current clinical approach by adding early diagnostic accuracy and reducing the need for repeated clinical examinations. When should PET be used? My answer to that would be to assist in the early diagnosis of dementia based on the evidence. And what would be the effect of using PET? It's clear to me that we would have more accurate and earlier diagnoses; the result would be better treatment outcomes. We'd have fewer unnecessary clinical assessments and we'd have earlier treatment when drugs are most effective. Thank you very much for your time.

MS. ANDERSON: Dr. Small, if you will stay for a second, we can have the panel address you with questions if they have any.

DR. LERNER: If PET weren't available or weren't on the table, you know, for coverage, as a clinician, what would you do, what would be the best thing you could do to diagnose patients earlier or better if you didn't have this tool?

DR. SMALL: Well, without PET, the best thing I could do would be to use the approach that

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the American Academy of Neurology has recommended, the standard clinical assessment where we get a good history, we use the laboratory to rule out treatable causes, and get an MRI scan to see if there is any identifiable lesions, so I'd use the standard approach as best I could.

DR. LERNER: Let me just take it a little bit further. The standard approach now doesn't get us where we want to go. Do you think this is an issue of better education of clinicians in the standard approach, again taking PET off the table, would you imagine that using the guidelines more effectively, you know, getting them actually used by clinicians would make a big difference to patients, or what -- what I'm trying to do is take it away from just the technical issue, asking a sort of broader question, what could you do to take care of the AD

patients in diagnosing them?
DR. SMALL: Well, there's many things we could do. Certainly education is a big issue. I've been involved and I know others here, colleagues have been involved in medical education programs for years. They are helpful, but as you can see from some of the data, they don't always have the impact that we'd like them to have. And whether we're using

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a standard approach or a new technology, there is always going to be an education gap. I know when I went to medical school, we had a paragraph in our pathology textbook about Alzheimer's disease and that was it. So we're dealing with a cohort of physicians that have a lack of education, so that certainly is something that we need to do, education is very important.
DR. LERNER: Let me try one more thought along these lines. Are there improvements in clinical workups through other research, behavioral research, that you think are in the wings that would give you an alternative way of getting better diagnoses now.
DR. SMALL: I don't. I think, certainly you have expert clinicians who are outstanding in identifying cases early on. To my knowledge, I don't know of another approach that can be used so consistently to get this kind of sensitivity and specificity.
DR. ALBERT: I have a question that relates to the question that I asked Dan before. I'm a little confused about the data in the Silverman et al. publication. As I read it, it doesn't look to me like it's about very early patients, it looks to

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me like maybe 60 some odd of the cases had mini-mentals of 20 or higher. Am I misunderstanding what the publication sets our?
DR. SMALL: I'll let Dan address that. And actually, let me go back to that. There was another question earlier about his data, and what

those data showed, we're basing it on a single baseline PET, okay? And when you look at the follow-up data, that is clinical follow-up, and so the question was, here's the baseline PET, how does that predict that clinical follow-up over the following years, so there was only one PET scan involved in all of those assessments, that's the first thing.
The second thing, in terms of the milder cases, I know that we did stratify the sample and look at the question in terms of people with mini-mental states 25 and above, so many of those people would have MCI and there would be milder cases. Dan, what number was in that 25 or above mini-mental state group?
DR. SILVERMAN: The sensitivity and specificity we looked at were just of the patients in the earliest stage of disease, and they were essentially unaffected; instead of 94 percent

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sensitivity it yielded 95 percent sensitivity, and the specificity went down like 2 percent, and the overall accuracy was about the same.
DR. SMALL: How many subjects had mini-mental states 25 or above?
DR. SILVERMAN: Actually the mean was about 24, and the median was two points higher than that.
DR. SMALL: So it was more than half.
DR. ALBERT: How many subjects?
DR. SMALL: There were almost 300 subjects, so we're talking about now over 100 subjects, maybe 110 were in the mild range.
DR. NEUMANN: Side effects of drugs loomed large in your remarks and are potentially very important in this decision. The Matchar model says as long as dysutility from drugs is not that great, .6 is the number they gave, as long as the dysutility is not greater than .4, treat all is still the preferred strategy. So you need quite of bit of dysutility from using drugs. Dysutility of .4 is typically much larger than you'd get from nausea and

GI side effects and so forth, so that's one question, just how severe are these side effects and what the implications are.

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And I guess another part of that is in your experience, are there many patients you are not treating with suspected mild to moderate dementia precisely because of the side effects?

DR. SMALL: Peter is testing my short-term memory and asking me a two-part question. What was the first part again? What about the side effects and --

DR. NEUMANN: You need a pretty big decrement in utility in the Matchar model to change the basic conclusion that treating all is the preferred strategy, so the question really is how big are these side effects and how important, and how much dysutility would they bring.

DR. SMALL: You know, it depends on how bad are the side effects, it depends on who's using the drug and who the patient is. I showed the data and they tell you something about that, those are from clinical trials, so we know that's not the real world, it's going to be different in the real world and in fact in the real world we tend to see things worse because we don't have such a pure sample, we have people with comorbidities who are taking other medications, and in fact the side effect profiles may be a little bit worse than what we see in some of

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those clinical trials. In my own experience there are people who do get quite uncomfortable and go off the drugs and do have problems with them. And in fact the idea of treating asymptomatic people, there are many asymptomatic people who wouldn't want to take these drugs; in fact, I know symptomatic people who are reluctant to take it and are concerned about it, so I think that's a problem with the assumption in terms of minimizing the side effects. And when we start talking about lots of people taking these drugs, it concerns me.

I mean my own approach, those of you who know my research, you probably know that my point of view or my basic theory or hypothesis is that Alzheimer's starts decades before we call it that based on our criteria, and right now I'm trying to test that hypothesis that maybe all of us should be on these drugs, but I'm not ready to go there until I have the evidence.
DR. LERNER: Can I ask a related question? Are there known bad drug interactions? Take your widow case who suffered from depression as well as Alzheimer's. Can you give both drugs, or what are the drug interactions?
DR. SMALL: Well, you can give both drugs.

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There are drug interactions. You know, there are the P-450 isoenzymes that tend to metabolize many antidepressants as well as the cholinesterase inhibitors, so drug interactions are definitely an issue we have to be aware of. We can do it, but we have to watch for it. And most older people who are at risk for dementia are on multiple medications, there's no question about that. Polypharmacy is a big issue in geriatric practice.
DR. LERNER: Sure. But in this case do you consider that? I mean, there is nothing special about those two drug interactions, what you would do for depression as opposed to Alzheimer's.
DR. SMALL: I was just giving that as one example but many of our older patients are on multiple medicines for physical illnesses and we have to be concerned about that as well.
DR. JOHNSON: You alluded several times to the cost of applying the accepted Academy model with respect to potential delays in diagnosis, repetitive evaluations and so forth. I'm wondering if you are aware of any data that actually attempts to quantify this with respect to number of individuals and length of time for which this may be an issue, potentially delaying treatment.

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DR. SMALL: Studies that have specifically looked at the delay in treatment, looked at that question, I'm not sure. Dr. Silverman, do you know a specific study that addresses that question?
DR. SILVERMAN: (Inaudible.)
DR. TUNIS: Let me make one comment and sort of a question and then a second question. The first comment is I think that the issue of primary care physicians not making the diagnosis of mild or moderate dementia isn't directly related to the question on the table related to the utility of PET, because if those folks aren't making the diagnosis, they are not referring people for PET, unless you are suggesting that PET be used as a screening tool amongst the elderly in which case it would detect unsuspected cases of dementia. But we're not really considering that as a coverage issue because Medicare doesn't pay for screening tools.
SPEAKER: The question is the clinical accuracy of the statement, it's (inaudible).
DR. TUNIS: Right, but if the primary care physician isn't suspecting mild dementia they're not going to be ordering a PET scan.
DR. SMALL: I'm not advocating screening, that everybody today has to go and get a PET scan.

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And even me, who forgot the two-part question of Dr. Neumann, not for screening, but I think it was to really put in perspective what is going on in the community, and that the gold standard of clinical diagnosis, the assessment is really not what's being used out there, just to put things in perspective.
DR. TUNIS: And the question I noted, so you're one of the authors on the Academy of Neurology guideline published May of last year regarding diagnosis of dementia, which specifically did not recommend using PET for the diagnosis of dementia, and I'm just wondering what information has accrued since that guideline was done that has either convinced you or convinced that committee of the utility of PET.
DR. SMALL: Well, the committee was very

strict on their evidence based approach, and if something had not been published in a refereed journal they would not consider it. And since that committee met and came about their conclusions, the publication that Dr. Silverman talked about or the data he talked about on those 284 patients collected from around the world actually, that was published in JAMA just a few months ago.
DR. TUNIS: So it would be the Silverman

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paper that would?
DR. SMALL: That's correct.
DR. TUNIS: And the Silverman paper, would it meet the criteria for a class one study?
DR. SMALL: Well, I think it would. That's why I put up those criteria up there in terms of a broad base of patients, in terms of a gold standard of diagnosis, blinded evaluation of the tests and so forth.
DR. TUNIS: So the Silverman study meets all those standards?
DR. SMALL: I would say so, yes.
DR. LERNER: Then is the Academy reconsidering its decision based on Silverman?
DR. SMALL: I have been in communication with some Academy members. I don't know of any formal process being initiated. I mean, these guidelines are reviewed periodically. The last time they looked at it, I think it was about six or seven years before that, so they may or may not respond quickly to these new data, I don't know. Not being a member of the Academy, I don't know.
MS. HART: I would like to ask about the costs of the conventional testing that's done as opposed to PET testing and I'm curious as to whether

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some or all of that testing is generally covered by Medicare now.
DR. SMALL: I was instructed not to talk about costs? Can I talk about it now.
DR. TUNIS: We'll stay way from that for

now.
DR. PAPATHEOFANIS: It's really not relevant to what we're trying to evaluate, but you may have a comment about coverage to address Sally's question.
DR. TUNIS: I'm sorry, can you repeat the question?
MS. HART: My question was about the costs of the conventional testing as opposed to PET and whether those costs are generally covered by Medicare now.
DR. TUNIS: They are generally, if it's, the testing of clinical evaluation as well as structural imaging, those are covered services under Medicare.
DR. PAPATHEOFANIS: Thank you.
MS. ANDERSON: We have a final speaker to conclude this portion of our agenda, and that is Dr. Peter Conti, who is indeed from USC, not UCLA, mea culpa. I would say that all California schools

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are the same, but my stepbrother, an alumnus of USC would say different. Sorry about that.
DR. CONTI: Thank you very much. It will be determined tonight on the basketball court. My name is Peter Conti and I'm associate professor of radiology at the University of Southern California and today am speaking for the Society of Nuclear Medicine. My personal conflicts are as follows: I do have some federal PHS support for research done with PET both experimental in existing radiopharmaceuticals. I have served on the speakers bureau for several of the manufacturers of both isotopes and commercial manufacturers of equipment, and I have received consulting fees from those as well. But as I said, I am speaking now for the Society as opposed to myself.
On behalf of the Society I would like to offer our strong support for the addition of Alzheimer's disease as a CMS reimbursable indication for FDG PET scanning. Right not more than 19 million Americans are estimated to be caring for someone with

Alzheimer's disease. In home care for a person whose disease has progressed is estimated to cost about $47,000 per year. By the middle of this century as many as 14 million of today's baby boomers could have

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Alzheimer's disease.
As you know, the standard wisdom is that there is no definitive way to diagnose Alzheimer's disease other than by brain biopsy or autopsy. The information compiled by the UCLA group and presented to CMS from studies all over the world in fact strongly supports the value of PET as an alternative diagnostic approach for this devastating condition. Recently the Journal of the American Medical Association also published an important study which we have reviewed today and I won't go into those details but in summary the study followed 284 patients through either long-term follow-up or autopsy for a confirmatory diagnosis of Alzheimer's disease. PET scans early in the dementia process demonstrated a prognostic sensitivity of 93 percent and a prognostic specificity of 76 percent; overall accuracy was thus 88 percent.
We believe that there are compelling reasons why PET is a valuable tool for physicians attempting to determine whether the memory lapses and behavior patterns seen in these patients are due to Alzheimer's disease or some other process. Number one, since FDG PET is more effective than clinical examination for the differential diagnosis and

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identification of various dementia causes, the greater accuracy provided by PET early in the course of a dementia illness will lead to more effective disease management. Secondly, PET enables physicians to clearly identify and differentiate between the types of dementia. This can be critical not only for treatment of these other diseases but for the initiation of Alzheimer's specific medications.
Third, notwithstanding the potential for therapeutic intervention, the usefulness of FDG PET is important

for patient quality of life. Specifically, additional certainty with respect to the diagnosis will help the patient and family make more appropriate life decisions. In addition, the increased certainty may help family members cope with the condition; for example, depression affects more than half of primary family caregivers and uncertainties about the diagnosis may contribute to family and caregivers' feelings of depression and helplessness. A negative study would be of value to patients as well as it can predict the absence of further cognitive impairment with fairly high certainty, which could well affect decisions the patient and family make about their future, retirement, moving or staying near home, not

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taking a cholinesterase inhibitor, et cetera. In short, the radiopharmaceutical FDG with PET can be used to assist with the characterization of early dementia in geriatric patients for whom the differential diagnosis includes one or more kinds of neurodegenerative disease associated with the dementia process. We believe it is particularly helpful in this population when there has been a change in cognitive status, when the etiology is not apparent, or when symptoms are not reversed in a reasonable amount of time. Providing families and physicians with the means to better manage those with this disease would seem to be a more cost effective approach to care. We believe this approach should include access to and reimbursement for PET scans. We urge you to agree with the many researchers whose work is presented today, and add Alzheimer's disease to the list of reimbursable indications for PET. Thank you for your attention.
MS. ANDERSON: Did the panel have any questions for Dr. Conti?
DR. NEUMANN: Just one question. You mentioned greater certainty which could lead to better compliance and other benefits. Are you aware of any data on that?

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DR. CONTI: I will defer back to my colleagues back at UCLA to answer that question if they would like to.
DR. SMALL: Could you repeat the question again?
DR. NEUMANN: The benefit of PET being talked about as greater certainty which would lead to, in addition to better general reassurance, better compliance of patients on the drugs, and the question was, is there any data to support that or studies underway that you know of to look at that?
DR. SMALL: I'm not aware of systematic data that have specifically addressed that question. I do know from my own practice and I think some of these issues have been alluded to earlier, that there can be a benefit in terms of having a better diagnosis, better compliance, and I have seen that in individual cases.
Another issue actually, since I'm on it, there is a possible downside of depression if people hear this diagnosis. And you know, yes, there's a lot of denial and people can be upset when they hear the diagnosis, but in clinical practice that kind of depression is generally minimal compared to and offset by the gains from early treatment and becoming

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proactive in intervening. So I have not seen that as a big problem.
MS. ANDERSON: All right. We're going to break for lunch and we are starting again promptly at 12:30.
(Luncheon recess from 11:36 to 12:36 p.m.)
MS. ANDERSON: We are going to open public comments. Members of the public are given the opportunity at this time to come forward to the mike and you will be given approximately three to five minutes to address the panel. I'm going to give everyone a little bit of time since we're just coming back, but no one signed in for public commenting, so we may move on from this point.
DR. SMALL: Could I make another comment?

I just had a few thoughts over lunch and just in case Dr. Neumann tests my short-term memory again, I have a couple notes here. I just wanted to emphasize a couple points that I made earlier and the first one is about the data that we have now from clinical trials and the kinds of patients we see in these clinical trials. These are selected populations, we want to get as pure a disease as possible, so the data I showed in terms of side effects, this is from these kinds of populations. So we screen out high

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blood pressure, screen out people on other medications and in fact in these trials, for every patient who gets enrolled we screen out about 10 or sometimes even 20, depending on the design of the trial, so that's the not the real world. And in fact in the real world, it's a much more complex difficult situation in terms of diagnosis and treatment, so I just wanted to emphasize that point, so we're talking about understanding diagnosis and using treatments in kind of complicated cases, patients with multiple medications.
Second point, I didn't say directly but I think it's worth making, and that is especially when we're talking about assuming that we are going to just treat everyone, assuming that there is no downside in terms of treatment, we don't know the long-term effects of cholinesterase inhibitor treatment. I mean if we just put people on these drugs in the long run, how is that going to affect us? This is a drug that will affect the entire body, all kinds of systems throughout the body, so I think that's a question mark. We don't know what that means and I wouldn't want to get into that unless we knew it. We do have data in terms of patients with

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Alzheimer's disease, open label data up to 98 weeks and even longer, and we know they're effective with those patients who need the treatment.
Another point I wanted to make again, try

to make a little more clearly, and that is the benefit of early diagnosis and early treatment. That's really where it's going to make a difference. We already heard about once somebody is in late stage Alzheimer's, what is that quality of life, do we really want to prolong it. So the earlier we can make an intervention, the better is going to be the effect, because really even though there are data now showing that even in some later stages you can have some benefits in terms of the health of the person, there's still that issue, what is the quality of life when you're treating at that stage.
And then the final point, let's put PET aside for a moment, let's just talk about diagnosis in general. As a clinician as I mentioned for 20 years in this area, we see these complicated cases, we need to do the best diagnosis we can. We didn't have treatments 10 years ago. The cholinesterase inhibitors have only been here for about a decade and in fact the first one that was introduced, Tacrine, had so many side effects that essentially it is not

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used anymore because of those side effects. But I remember those days when we didn't have much to offer except for supportive care, looking for other treatments and so forth. It was critically important for the patients and the families to know what the diagnosis was. I mean, who of us here wouldn't want to know an accurate diagnosis if we had that opportunity to find out. I think most of us here would want to know, so I think the value of early diagnosis aside from the treatment implications is something that's very important for the physician, important for the patients and important for the families. Thank you.
MS. ANDERSON: Actually for the record, if you would state your name again.
DR. SMALL: My name is Dr. Gary Small and I am at the University of California at Los Angeles.
MS. ANDERSON: Thank you, Dr. Small. At this point I guess we're concluding the open public comment period and the panel will begin

deliberations. From this point forward there will be no public comments unless specifically requested by the chairperson.
DR. PAPATHEOFANIS: Great, thank you. I guess it's just a matter of revisiting the charge of

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the panel, which as all of you know is the voting question basically, and that's been stated very specifically in the handout that you all have. Basically, is the evidence adequate to demonstrate that PET has clinical benefit in the patients we have been considering.
I think what I would like to do is just open the floor to discussion and as you all know, we have an ad hoc group, if you will, of visiting attendees who've got terrific expertise in these areas both from a clinical perspective and from a methodological perspective and so if you choose to, please avail yourselves of those experts.
DR. McNEIL: Frank, could I just ask one request, that before we vote, would it be possible for Samantha to put up the two criteria against which we are supposed to make our judgments, the ones that she had in her opening presentation. She doesn't have to do it now, just so we have it when it comes to the voting period, so we know what evidence we're supposed to be counting.
DR. PAPATHEOFANIS: Sure. And we could actually, as soon as she has a chance to put that up, we could just even put it up now and leave it up.
DR. TUNIS: Also, I want to remind the

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panel that if you have additional questions or if the discussion leads to a point where it would be useful to have input from either Dr. Matchar, Dr. Zarin or other of our speakers who are still here, that it is perfectly permissible to request that they come back to the podium and you ask them a question. So to the extent that you want to do that as part of your discussion, you're open to inquire of them.
DR. PAPATHEOFANIS: Okay, terrific. Well

then, let's vote.
(Laughter).
DR. LERNER: Can I just ask a question about the side effects issue. Under the treat all strategy, you would still get the same percentage of people who go off treatment because of side effects, so I was wondering why that other argument was important if our frame of reference is the assessment that seems to have accounted for that. Does anyone disagree with that?
DR. NEUMANN: Well, the other problem would be if you have side effects, you have dysutility, so you're going to have fewer qualities gained, the more side effects you have.
DR. LERNER: So you look for the aggregate.

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DR. NEUMANN: Yeah.
DR. TUNIS: And maybe just to make a point on the side effects, and I want to make sure I'm interpreting this correctly, that under the strategy of obtaining a PET scan prior to making a decision to treat, and Dr. Matchar, you can address this, the specificity of the PET scan overall, I forget in the model if it was 70 or 80, aggregate specificity. So whatever the difference between that and 100 percent, that would represent the percentage of patients who would also be inappropriately treated under a test and treat strategy. So even under a test and treat strategy you're still exposing some fraction of patients to the dysutility of side effects and that number is whatever we accept to be the specificity. Versus in a treat all strategy you would have that dysutility for 35 percent of patients or whatever -- for the treat all strategy, what's the percentage of patients that would be so-called inappropriately treated with the anti-Alzheimer's drug?
DR. MATCHAR: There is a distinction between, or there's several kinds of complications one can have. There is the kind of complications we were talking about in the base case model in which patients experience some bad effect and it's

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transient and they stop the drug, and then there can also be a longer term effect and that can last for a period of that cycle or for the rest of their lives, and the model permits those things.
The kinds of complications we were talking about in terms of these dysutilities, they were prolonged side effects, these were not going to just necessarily be -- so these were big deal complications, these had to be drugs that were really bad.
Now to specifically answer your question about in the treat all strategy, what that means is that you know, if you're saying your prior probability of a patient having Alzheimer's disease or treatable diseases was 55 percent and then we used a sensitivity of 86 or 87 percent, and a specificity of about the same, so they're all in the same ball park, we are all in kind of agreement about what the operating characteristics of the test are, that if you treat all, then 56 percent times the sensitivity of the test is the proportion of patients who are going to be, of 100 percent of patients, the proportion of patients who are going to be correctly treated.
So if you take -- so which number did you

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want, you wanted the number of people who are unnecessarily treated? People who were unnecessarily treated would be the people who didn't have disease, so that would be 44 percent times the specificity of the test, so it's of the people -- I'm sorry, 100 minus the specificity of the test, so it would be 44 percent times 13 percent, so whatever that comes out to, so that's around 4 or 5 percent, so about 5 percent of the patients would end up being unnecessarily treated, being subject, so five out of every hundred patients would be subjected to unnecessary side effects of treatment. So it's a fairly small number but it's not zero.
DR. LERNER: And then they just go off

treatment?
DR. MATCHAR: Right, if it's a benign drug, that's the core of the conclusions is that that 5 percent of people, it's not only relatively uncommon, but it's also of relatively little consequence.
DR. SILVERMAN: Could I add to that? If I understood your question correctly, it was given the treat all strategy, what proportion would be incorrectly treated, and the formula he just gave --
DR. PAPATHEOFANIS: Dr. Silverman, can you

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hold on for just a second. We're trying to keep the discussion to the questions that are coming from --
DR. SILVERMAN: I'm responding to that question.
DR. PAPATHEOFANIS: You haven't been asked to respond to the question. This was a question directed to Dr. Matchar. Is that basically what you were asking?
DR. LERNER: I'm fine.
DR. PAPATHEOFANIS: All right. Anything else that you wanted to go into as far as the side effects, especially if we can get at dysutilities in a more quantitative way. I guess I would leave that more up to the clinicians who actually take care of these patients to give us a sense of whether that has been represented accurately according to your experience.
DR. ALBERT: Yes, it's my general impression that the side effects have been appropriately represented. They tend to be mild, as Gary indicated. The most disturbing one is, are GI symptoms, and they ten to either be eliminated completely or be reduced by the way in which you administer the medication. So if you very gradually increase it, you will lower the likelihood of having

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those symptoms. And by in large, the number of people who discontinue it because of they symptoms is exactly as it was described, about 15 percent.

DR. PAPATHEOFANIS: Is that okay?
DR. LERNER: Yeah, absolutely.
DR. PAPATHEOFANIS: Dr. Johnson, did you have anything to add?
DR. JOHNSON: That's my experience as well.
DR. PAPATHEOFANIS: So the model holds and so forth. What Barbara asked for has been posted, I believe the two points that lead into the question we're going to be voting on, and that is whether or not the evidence regarding the accuracy of PET in this case compares with standard methods of diagnosis, and then of course the impact of this improved accuracy on net health outcomes. Did anyone want to go into either of those points?
DR. McNEIL: No, I just wanted them up there.
DR. PAPATHEOFANIS: It's a good frame work to sort of build a conversation around.
DR. LERNER: I guess the biggest question I have is did anybody on the panel here, if we're basically satisfied with the model that was

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presented, did you hear anything that gives you pause about the model, in essence the first question above the voting question, does anyone have some major qualms?
MS. ANDERSON: For the record I am going to read that question just so we have it. The question that we're referring to is, is using the AHRQ decision model, including its assumptions and calculations, a reasonable way to determine the clinical utility of PET as an imaging tool in the diagnosis and management of Alzheimer's disease? And then it goes on if we have a decision.
DR. ALBERT: It may be worth stating that at least in my opinion, the model seems to be generous in the sense that it accepts a lot of the literature and doesn't get overly upset about whether or not the case mix in any particular paper is appropriate and like real life, things of that sort, I think it tends to be quite generous. Whether or

not the data are always interpretable, you can always look at a scan and come to a conclusion about what pattern it shows.
DR. PAPATHEOFANIS: Peter, would you agree?
DR. NEUMANN: I would say overall I think

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it's a very nice model structurally and I think the assumptions made are reasonable, the sensitivity analysis around the parameter estimates, and I would agree, some things may be generous, perhaps in terms of the drug effect, believing that the drug effect would last for that long, that dropouts are rather minimal, that the drug works in MCI and symptomatics, perhaps that is a bit optimistic.
On the other hand, there might be other benefits to the drug that are not considered here. Caregiver benefits for example, nursing home admission for example, and again, there is a sensitivity analysis around the effect of the drug that shows that the basic conclusions are fairly robust. I mean, it's narrow but robust that treatment is preferred.
I think there are two big areas of uncertainty. One is -- well, maybe three areas. One is do the drugs work in MCI and asymptomatics, there is no formal evidence on that; the drugs haven't been approved for those indications. Two, side effects of drugs as has been mentioned and long-term effects as was just mentioned, there is no evidence long-term on what happens. And the third area to me that the public comments really get at and is not quantified

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in the model, though alluded to as an important potential issue is the value of the information.
The one place the test strategy does better is the percent correct diagnosis. It doesn't do better on life expectancy or qualities or percent dementia free states. It does do better, 87 percent versus 56 percent, on percent correct diagnosis. Now what's the value of that additional percent that you

have of good diagnosis on? I think that's the issue and I think what we heard is that clinicians believe that that would lead to better management, more reassurance on their part, more reassurance on the part of patients, maybe better compliance and so forth. But I think then we're into an area of speculation without a lot of data.
DR. PAPATHEOFANIS: So you think the assumptions that were made were possibly a little generous but because we don't have direct evidence, that they are reasonable?
DR. NEUMANN: I think so. And we can quibble with, there's lots of assumptions that go in, we can quibble about them. I don't think they're going to change the basic nature of these results.
DR. PAPATHEOFANIS: Okay, that's important to know. Anyone else want to add in?

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DR. TUNIS: I wonder just as part of this -- well, Sally, why don't you go first?
MS. HART: I was just going to say as the consumer representative I have some concerns about the focus of the model on treatment decisions that might be made in response to a correct diagnosis. I think beneficiaries, I think I can fairly say are interested in knowing their diagnosis in order to make important life decisions and that that's an important factor, should be an important factor in our decision making, as well as how effective treatment decisions will be.
DR. TUNIS: I guess the point I was going to raise and more to see if the committee is satisfied with their understanding of it is that there seems to be discrepancies in the outcomes of the model presented by the Duke folks, Dr. Matchar, and the model more briefly presented by Dr. Silverman, and we explored that, tried to explore those differences a little bit, but I'm just wondering if given that these are both decision models also and they seem to come out with fairly radically different conclusions about the impact on health outcomes, particularly regarding fewer nursing

home days, whether we ought to try to explore a

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little bit more the sources of the divergence in the conclusions of the model.
DR. NEUMANN: I guess I don't really read it that way. I mean, I think the models look at different outcomes essentially. Where the Matchar model looks at quality of life expectancy gains and percent in severe dementia free states, the Silverman model is really looking at -- well, there is some differences on sensitivity and specificity, but the outcomes looked at in the Silverman model are really months with unnecessary drugs and I think if you, the Matchar model could certainly accommodate that and you would probably come to some similar conclusions. Now nursing home placement is looked at by the Silverman model, not in the Matchar model, but my strong guess is if you really took the Silverman model and compared test versus treat all even with nursing home days, treat all is going to do better under reasonable assumptions. I don't know if anybody would disagree with that but you'd have to really convince me that that's not the case. So I don't see the models coming to very different conclusions. They do come at the problem in different ways, they do look at different outcomes, but I think they are sort of taking a

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different angle on the issue.
DR. TUNIS: Maybe just a question, and I wonder, Dr. Matchar, if you wouldn't mind talking about the issue of the nursing home days saved as an outcome in terms of how you understand it from the UCLA model, and then maybe have Dr. Silverman have a chance to respond to that. Do you feel like you know the UCLA model well enough to comment on that aspect of it?
DR. MATCHAR: I think I would be doing a disservice to the committee by trying to make too much of my understanding of the model that was presented this morning. I mean, I agree that it is

possible to use something like nursing home days as a surrogate for what would the more standard kind of policy analysis measure which would be a quality or a life year. So it didn't quite compute for me why the testing strategy should necessarily lead to more nursing home days, or fewer nursing home days if indeed everybody was going to get treated, and I think that's what everyone is discussing, that as long as that scenario is not being considered, then that's the explanation. If they were to consider that option, then we would probably have substantively the same conclusions that they would

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conclude that everyone for whom treatment is effective should be treated.
DR. TUNIS: Dr. Silverman, could you respond to that please?
DR. SILVERMAN: Thank you. Yes, I actually agree with Dr. Neumann, that these are not substantially different predictions that would arise from the two models, that they come to basically the same conclusions, pretty close to accuracy of the PET. And also, I agree with Dr. Matchar that you can use a surrogate -- it wouldn't be a surrogate for life expectancy, what it would be a surrogate for would be the severe dementia free period. And I also agree with Dr. Matchar that yes, if you measured against the treat all strategy, which is not what our model purported to do, that you would get a comparable conclusion there. And what our model did is measured against what actually has been done in clinical trials, which is treat patients according to whether or not they are thought to have Alzheimer's disease by NIN/CDS/ADRA criteria, not by a treat all strategy, and we compared what would happen if you treat them according to the diagnosis whether or not they have Alzheimer's disease as made by those criteria by themselves versus as made by that kind of

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diagnostic workup with PET incorporated into it.
DR. PAPATHEOFANIS: Thank you. Peter, are

you aware of any other models floating around there?
DR. NEUMANN: I have been involved in some modeling, not specifically looking at PET I should say, not yet, it could easily be accommodated to do so, but the modeling that I have done is basically similar to the Matchar model; it's a mark-off model that follows cohorts of patients through stages of disease and follows utilities and life expectancy and so forth, so -- and it's a big reason why I feel comfortable with the model. And there are others out there that basically do the same kind of things.
DR. PAPATHEOFANIS: That's what I thought. Any more discussion around the model? The reason we're beating this horse into the ground is because as you can gather, it's at least according to Sean probably the first time that this sort of model or decision analysis, which has really grown from the interim guidelines that have been put together by this committee will be used to drive the decision that comes from this panel. So it's important that we are all comfortable with the ins and outs and crossed every T and dotted every I before we consider a vote.

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DR. TUNIS: I think it would be useful actually if we could maybe even just poll the entire panel on sort of their reaction or response to question number one, which is you know, is the model including its assumptions and calculations a reasonable way to determine the clinical utility of PET, and at least give everybody a chance to reflect on that question, and I think we will do this with all these general discussion questions.
DR. PAPATHEOFANIS: And then move on.
MS. ANDERSON: Just to clarify, are we calling for a quasi-vote or just comment?
DR. TUNIS: No, just comments.
DR. PAPATHEOFANIS: Sally, why don't we start with you. Anything that you want to add on this discussion so far?
MS. HART: I already made the point that I'm concerned about the sort of inexorable link

between diagnosis and treatment options because I don't think that that's the only valid way of evaluating the work of a diagnostic tool. I also have some concerns about the practical efficacy of the treat all approach, although I understand there is a difference of opinion about that. I don't see strong evidence to support the belief that it is

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reasonable to assume that physicians and patients will function that way, and so I have concerns about that part of the model as well.

DR. JOHNSON: I have to agree. I think as Dr. Matchar said earlier, there are some limitations and to some extent the model is incomplete, although many other aspects of the problem could be included in the model. Whether those limitations are sufficient to make the model, to compromise its utility, I think the answer would probably be no. Clearly we'd like to know more about the costs, not necessarily in dollars, but in delayed diagnosis that could be involved in using the standard practice rather than a one-time study. And we would like to be able to know what it means in dollars or in healthcare outcomes to know a diagnosis with certainty. I think if you could put those two features into the model, we would have a better model; whether that information would be sufficient to change the overall conclusion, I think probably not, but that's just a guess. I have no data to support that.

DR. PAPATHEOFANIS: Jeff.

DR. LERNER: I am comfortable with the model as presented and discussed and if I could just

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editorialize for a moment for the public benefit, I think that since it plays such a central theme both in this discussion and clearly for future ones, it does raise issues about how we can get the best critiques of models from public comment so that, you know, so they will be most critical in the best sense of the word. And I don't know, you know, what

strategy invites you to do that, but I think Medicare should do something.
For example, there could be either some guidance issued to public presenters or you could take some educational course on this type of modeling, on mark-off models, and help people understand how they can make critiques of the models, both generically and then of course you have to apply that for the specific case, because Sally, you raised a couple of issues that are certainly true issues. The problem that we have is understanding research data that would cause us to overturn the model or to adjust it in some way. And we have instincts that maybe some of those things are important but we don't have data and we're supposed to be data driven.
DR. PAPATHEOFANIS: As far as the panel is concerned, the reason for bringing aboard the ad hoc members was exactly to address that, that someone

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like Dr. Neumann who has more than a course under his belt can really spend some substantive time and answer substantive questions, and of course he's available to the public as well. So I think it's a good point that you're making but we can't expect everyone to understand very sophisticated models like this, and that's why we have this forum, it's an opportunity to ask some questions. But as far as asking more sophisticated questions, I think you're right, the more education that's out there, obviously the better the questions. Barbara.
DR. McNEIL: I think this is a very complicated case. I actually thought that the model was a very very good one and I thought that it was particularly valuable because it really ran the gamut of all the possible variables that affected the decision. The assumption is that we do testing, because largely the assumption in this model, and I think in most of medicine, is that we do testing to drive management and treatment decisions. If we were to say that testing is done for the goal of information content per se, and that we could attach a higher utility to that information, then we would

be talking about a completely different ball game in terms of how this committee operates.

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It was my impression where I am, people generally do testing for the purposes of treatment, so that's why I am supportive of the model. But following on one thing that Jeff said is for future discussions of this sort, we ought to get the opportunity to really dig into the Duke model very very carefully, it actually took a long long time to do, and it seems to me in the future, if this is the way of doing it and there is a public presentation of a different model, then it's probably most important to indicate exactly where it differs. You know, have the base line tree up there and say we differ in decision node two and we differ in outcome six.
DR. PAPATHEOFANIS: Be specific.
DR. McNEIL: Be very very specific because otherwise, I don't think it's easy for us, without having something written much more so than the limited review that was given, to make a comparative view. In this particular case I don't think it matters because of the treat all strategy, but if it did make a difference for other reasons then I think we would want to have some way of getting that other than from a ten-minute presentation.
DR. PAPATHEOFANIS: As another person here who has more than a course under their belt and your

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allusion to the treatment intent of this sort of modeling, did you see any weakness, or I guess the question is, are you comfortable that this is a reasonable way? I mean, of course there's going to be limitations and weaknesses and so forth, but is there anything that jumped out at you with your experience in using those models and taking this treat all approach that maybe you want to bring up at this point?
DR. McNEIL: Well, no. Actually I agreed with it as I said, Frank, and I actually had a mother who died of Alzheimer's disease, and if I were to put

her in this decision node right now because of the false negatives and the potential treatment benefit, I personally would go with the treat all on the basis of the data without even going through this complicated a model. This is almost the kind of thing that once you believe that you need a treatment outcome, I hate to say it, but it's almost obvious, you don't necessarily -- right?
SPEAKER: Yes.
DR. PAPATHEOFANIS: Thank you. Peter.
DR. NEUMANN: I would agree with those remarks and I guess just add a few things. This is a very complex issue and despite the intuitive nature

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of it, I think it's very helpful to go through a model like this to really understand sort of the intuitive appeal in some curious sense. The model does lead to this very interesting result that it's better to treat everyone, and that will result in treating a lot of people who are not treated today and treating people for whom we don't have the kind of evidence we would like to have from well controlled trials. So I think that needs to be on the table and thought about.
The model also has this interesting result that a more and more accurate test is not going to change the basic conclusion. Treating everybody is still better as long as you buy into the assumption that the side effects are not very bad, so that's also interesting. We can talk all day about how accurate this test is and you know, you can present data that it's more accurate than is in this paper, but it's not going to change the results if you buy into the conclusion that the side effects aren't very bad.
The one place I would come back to that I think is important and comes out of remarks by Doctors Small and Silverman, how much is it worth to have a better diagnosis? Perhaps the answer is not

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very much, treat regardless.

But there are data out there, even from Alzheimer's the little bit that I know of, but certainly from other diseases that people, physicians, patients, family members value information. Even if they don't do anything about it, they may value that information. And certainly in this case perhaps they would do some things differently if they knew it were Alzheimer's disease, perhaps better management we heard about today and so forth. So I think those are important issues that could potentially change the results. If you really believe that information were very important, then you might want tested, but that's not explicitly considered in the model. So I think the model is a rather nice one, but I do have that issue.

DR. PAPATHEOFANIS: Okay. Marilyn.

DR. ALBERT: I concur with most of everything that has already been said. I do think that the model is a good one, I think it's generous and has already been said, when we have better treatments, they will no doubt have more side effects and then we will revisit this. We will revisit it hopefully with more information about the accuracy of various tests that are available and with more

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information perhaps about the value of just information per se, and perhaps we could build that into the model as well.

DR. PAPATHEOFANIS: Okay, great. Kim.

DR. BURCHEIL: I think it's pretty clear to me that PET is an accurate test. I think the thing that's hanging us up is the data on outcomes is lacking. But the thing that I guess bothered me a little bit about the model is that the treat all strategy, is that really data driven? I think it's actually the reverse, it's sort of driving the data, it's driving the model. It's a bit of an artificial construct.

As Peter just pointed out, this is not just an implicit part of the model, this is a treatment recommendation, and I am concerned that that's sort of ingrained in our deliberation right

now, is that we're really talking about a new treatment recommendation which is not, maybe the neurologists can correct me, but it's not part of the AAN, it's not a guideline, it's not even on the radar. So is this feasible, is it practical, those issues have been brought up. It's certainly never been tested, so if we're a data driven deliberating body, we don't really have data on that particular

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thing.
I don't think that that completely subverts the intent of the model, I think as much as I understand the model. But I think we have to recall that this is not a real situation; we're really talking about a major clinical recommendation that is as unproven as PET is in terms of outcomes.
DR. PAPATHEOFANIS: Steve.
DR. TUNIS: I think what we're going to do since there will be probably some desire to respond to these, that we will invite a few folks up to respond to these specific comments once we get through the whole panel.
DR. GUYTON: I would echo Kim's concerns that both the treat all strategy and the test strategy, which are basically compared in the model, neither are based on present day reality, and both are a significant change from what is going on in clinical practice today, and if CMS wants to say in response to a request for PET scan no, I'm sorry, you need to treat the patient, then there are going to be a certain number of patients who are going to be treated outside of the FDA labeling of the drugs. And who's going to be responsible for that.
So, I agree that the model seems very good

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and comes to some conclusions that are probably important for the American Academy of Neurology to consider, but we're not at that point yet.
DR. PAPATHEOFANIS: Carole.
DR. FLAMM: I think overall I have a significant comfort level with thinking of this in

terms of the model that has been presented. The sensitivity analyses that were reported do show such a nice robustness to the conclusions over the sensitivity range that needed to be considered in the diagnostic performance and the treatment efficacy and side effects. I too, we sort of struggle with this idea of the value of information and whether that can be studied empirically and try and quantify and roll that into some sort of quality of life sort of measure would be an interesting direction and that would be something nice to see to sort of start to consider that explicitly.
As far as the practicality and whether in real life people will treat all patients, I don't treat these kind of patients so I don't know, but I think that is something that we would need to think about in terms of how applicable this would be to real life applications.
DR. PAPATHEOFANIS: Okay. Dr. Matchar,

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and then Dr. Silverman.
DR. MATCHAR: I would like to apologize for having named this strategy treat all, because I think I may have led to a misperception of that meant. The treat all strategy again in the discussions with our advisory group, was to treat individuals, and we're only talking for the true base case or for the demented patients, patients with mild to moderate dementia. Treat all meant those individuals with mild to moderate dementia who have a probability of having Alzheimer's disease on the order of 50 to 60 percent, that treating all of those people who have dementia of that sort is superior to testing them and only treating people with a positive test, again because the people who were false negatives would fail to be treated.
That actually, my understanding is that from the perspective of experts in the field, that is the recommended practice, so the treat all strategy of people who clinically have dementia who have no other evident reason for being demented, reversible causes and so on, that those individuals will be

treated, that's fairly common practice. And the only reason people don't treat is because the patient doesn't want to pay for it, the doctor doesn't think

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it's all that worthwhile, or some combination of those.
The issue about the treat all strategy for the other two scenarios, those were pure speculation, and we acknowledged that those were pure speculation, and the only reason that we evaluated those was because we were asked to evaluate them. We acknowledged up front that there was no evidence that treating all patients with mild cognitive impairment or treating all patients with first degree relatives, that there is no evidence that treating those patients makes any sense. So the model in no way suggests that that's the right thing to do; the model only suggests that if you believe that treatment works for those people in delaying the onset of dementing illness, then you should treat people. So there is a big if.
And then the last part is the value of information question which I think is a really important point, it's something that's very difficult to incorporate into an analysis like this, but effectively the way I look at that is as follows: You incorporate into the model the things that you can quantify reasonably well. Life expectancy certainly, quality of life with the cognitive

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impairment maybe not quite as well, but these issues of value of information even less well. Now if we don't include the value of information in this analysis, the question you need to ask yourself is whether the value of information is worth the decrement in life expectancy or quality in life or dementia free survival, is the information worth it to you to get that information, acknowledging that if you do get that information you may actually lose life expectancy or lose quality of life.
So yes, it's something that needs to be

studied empirically and if there were empirical evidence about that, it could be included in the model and should be included in the model, but in the absence of that, there is really no way to handle it other than just subjectively, is it worth that trade-off in quality of life or survival.
DR. PAPATHEOFANIS: Does that help clarify the question on treat all?
DR. BURCHEIL: Yes.
DR. ALBERT: Could I just make one comment? In fact what's going on in clinical practice is that people who have so-called mild cognitive impairment are also being treated with a high degree of regularity and it is specifically

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because the downside is very small, because nobody knows, they have the hypothesis that it might be beneficial and people want to preserve neurons if they can and the downside is small, so in fact that is what's going on in clinical practice to some degree.
THE WITNESS: So you would agree then that Dr. Matchar's recommendation or suggestion that treat all is a misnomer should really be reclassified as folks with mild to moderate cognitive impairment?
DR. ALBERT: Well, what he's talking about is true, that people who meet criteria for probable dementia, which is still an uncertain diagnosis, are recommended for treatment, and people who are even milder than that are offered treatment, at least in our practice.
DR. PAPATHEOFANIS: Dr. Silverman or Small?
DR. SMALL: Just a couple points I wanted to make. One, I think that Dr. Matchar said that the current practice is to treat all patients with dementia and Dr. Albert mentions a lot of MCI patients are treated as well. That is the case. A lot of dementia patients are treated and a lot of MCI patients, but the indications right now are for mild

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to moderate Alzheimer's disease. So these are really off label uses of these medications.
But the point I wanted to make and I don't think it was mentioned as yet, and that is if you accept the assumptions and you look at the logic of the model, the logic is not only that we should recommend treatment for everyone, but we shouldn't be doing any diagnostic assessments. I mean, why should we do that? We're saying, our assumption is that let's just treat everybody, there is a possibility it may help. We've extended the model to people just with a family history of dementia, right? What if we extended that to just people. I'm not an economist, I'm just thinking the logic of it to me says we should stop doing clinical examinations, we should stop doing PET scans, and we should just put everybody on cholinesterase inhibitors, and to me there is something fundamentally wrong with that logic.
DR. PAPATHEOFANIS: Dr. Matchar, or Dr. Zarin, could you address that?
DR. ZARIN: If I could, I would like to address that and then say something else about the value of clinical information.
DR. PAPATHEOFANIS: Sure.

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DR. ZARIN: I think that again, to reiterate what Dr. Matchar said, the treat all strategy for the mild dementia was really developed to reflect current practice. These are people who after they have gone through the AAN standard workup are presumed to have Alzheimer's disease. The question we were asking was, should we do yet another test to try to increase the certainty that they have Alzheimer's? But these are people who clinically today, to go back to Dr. Lerner's scenario if PET didn't exist, to the best of our ability we think they have Alzheimer's disease, and that's who is recommended for treatment with the cholinesterase inhibitors. That's what the treat all strategy is.
Again, for the other scenarios, it was this huge if. If you believe that the treatment

trials will eventually show that the drugs are also effective in those other groups, so that if you believe treatment works, then increasing diagnostic certainty won't help you any. Because again, the people you're going to save from treatment, the sort of true negatives, will be outweighed by the false negatives, the people who really would have benefitted but are now not going to get the treatment. So that's the -- treat all is an

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unfortunate term but anyway, we have hopefully undone that.
In terms of the value of clinical information that is not modeled, if you look at Table 10 in the technology assessment, we really tried to at least brainstorm and look at the literature on sort of psychosocial and other ethical impacts of diagnostic information, and I think it's important to realize that there is potential positive impacts and potential negative, and in order to be sort of valid about it, you have to think about it both ways. So you can think about the people with MCI who might be harmed by having the label in their medical records saying they have Alzheimer's.
I mean, they could be harmed in terms of insurability, employability, et cetera, things like that. You can also think of the way in which they might benefit. I mean, they're going to get a treatment that they otherwise wouldn't get. And you can go through it, and we tried to at least systematically think through, do the thought experiment of ways in which people might benefit or be harmed. There is no data that we know of to tell you on balance, but my guess is that it's going to be heterogeneous, it's going to vary with different

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people's particular situations, with their own utilities, et cetera.
I think it's worth looking at that table, because I think you have to remember the negative value of information in both the true results which

could have a negative impact, and certainly the false results.
DR. PAPATHEOFANIS: Thank you.
Dr. Silverman, did you want to add to that?
DR. SILVERMAN: Actually, there is a lot that has been said both by the panel and by speakers after the panel to respond to. Let me start with kind of the end, and treat all is an unfortunate terminology for the people in the mild to moderate dementia category, but it's not an unfortunate terminology, it's a very accurate terminology for what they're doing to people in the MCI category. Basically what's happening is they only need to have enough symptoms to document that they have memory impairment without necessarily functional decline to put them in the treat all group.
Now, I think that Dr. Burcheil's and Dr. Guyton's points were really right to the point, which is that the panel is polled about how do you feel about the model, and I don't think anybody

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disagrees that the model is a very fine model in many ways, in terms of its structure, in terms of the ways that it arrives at its estimates with which to fill the structure. The problem is what questions the model is being used to answer, and the question it was being used to answer was not the question that was given to it. It was not being used to answer the question of what happens when you use PET versus when you don't use PET in terms of clinical outcome, it's what happens if you use PET versus if you treat all or if you treat none.
And if you think about it, you know, this is supposed to be a technology assessment, but if you think of it, if you had a two-sided coin that was both side heads or both sides said treat, and you flipped it, it would be a totally useless test in the sense that it had no relation to reality, you would still end up with a better outcome than you would with another test, PET or anything other, that had 99 percent sensitivity. So it ends up not being an assessment of the technology at all, it ends up being

an assessment of the treat all strategy, which isn't what the committee was charged to answer. Secondly, Dr. Hart raised a very good point about the importance of information and that

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was echoed by several members of the panel, but it goes beyond just any kind of touchy feely yeah, it's nice to know. There's actually hard data; there is, for example, an excellent randomized control trial by Mittler that was published in JAMA in 1996 before the era of treatment with anticholinesterase was popular, and that looked at specifically the value of having information in terms of plugging patients into proper resources in terms of counseling the families with what to expect and so forth, and they found that among those patients who had mild symptoms that there was an 82 percent reduction while they were in mild symptoms of nursing home placement, and delayed for the whole group overall nursing home placement by 11 months. So that information can be used not just to make patients and their families feel better about knowing the answer, it can actually be used in ways to treat other than anticholinesterase treatment. And the model only answers, not only asks the question about PET versus treat all and treat none, it only answers the question about PET treat all with anticholinesterase versus treat none with anticholinesterase, which is a very limited question for the model to pose. And finally the issue about labeling

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patients, whether it's labeling them with technology or labeling them with a diagnosis, if you label them with the diagnosis made just purely clinically, as you saw from the lower specificity, you will actually mislabel more patients as having Alzheimer's disease than if you used PET to establish that label. On the other hand, if you treat all, imagine the labeling that's going on here. You have every patient who has MCI and they have to say oh, I'm taking Donepezil or Rivastigmine or Galantimine and you say why are you

taking that, well, my doctor thinks I might have Alzheimer's disease. I mean compared to having a PET scan and saying oh, I can say with 95 percent certainty that even though I have the familial problems, those aren't due to Alzheimer's disease. And I will stop at that point, thanks.

DR. PAPATHEOFANIS: Thank you. Jeff.

DR. LERNER: You know, I really find this to be an absolutely fascinating discussion, and I wonder in terms of since we will be using these kinds of models at MCAC whether the EPCs from AHRQ might be able to take some of the things that are in Table 10 that build on some of your arguments, Dr. Silverman, and in a sense reduce them to social science to the best of our ability, because if decisions like this

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are going to turn on this in the future or at least turn part on it, you can see the scenario of today repeating constantly with no evidence, just lists of things that could be or could not be. There needs to be a sort of social science of how patients make decisions, how doctors make decisions, how they change clinical practice. Now obviously people are working towards that, but maybe it needs to focus some on some of these major technologies that we're asking for because we're asking for national coverage decisions that have you know, such a huge impact, so it's worth focusing that kind of research on these kinds of questions.

I would assume that's where we may try to get to in the future, but a lot of these are research questions and I was sort of stepping back and saying there's different world views going on here today, very different approaches. One is the value of knowing, human curiosity. Clinicians have it, medicine has always been built on it, patients have it more and more. And those are various serious research questions and were this a research panel, you know, you'd discuss it for quite a bit and you'd commission all kinds of studies. But it's a coverage panel and it's asking does the evidence exist today,

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now, can it be presented at this moment that will inform our decision, because we have to make decisions based on available evidence today. So that's where I think the world view is sort of a tough issue, but I think there is a way to make some progress.

DR. PAPATHEOFANIS: Well, I think one of the recommendations I would like to make to Sean and we will probably pursue this off-line is to try to enlist the help of folks like Peter and other methodologists on more of an ongoing basis and maybe form some sort of ad hoc subcommittee of the Executive Committee or something along those lines if we're going to be thinking of using modeling in the future for further assessment and part of that will be, again, the education opportunity, whether web based or individually based or how we decide to propose it, to bring as many people up to speed as possible. But I think you're absolutely right, there are national meetings and journals, international journals focused on these issues of methodology and we're not going to resolve them here. And certainly the point that you echoed that we are facing with making a decision based on the available evidence is true. We just have to all be comfortable with what

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we have in front of us, and that's what we're all hoping to get into this, or out of this round of conversations.

I think I would like to move along though, and that is to question 2, in keeping with that focus. We have addressed some issues that were not addressed in the model but might influence our decision. Are there any other issues apart from those we have already come up with that have not been addressed by the model that any of you would like to discuss or bring up at this point? Marilyn?

DR. ALBERT: I just think it's worth noting that if it were the case that PET identified a fraction of patients who responded to treatment better, then that would change the way in which we

were balancing things, but to my knowledge there are no such data, but that would be one way in which actually knowing would make a huge difference.
DR. PAPATHEOFANIS: I'm not going to poll everyone on this one again. Did you have a comment, Sean, on this question?
DR. TUNIS: No. I think in the previous conversation we have identified some of these other issues outside the model that we think are relevant and important for CMS to consider, and I just wanted

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to make sure this is not a final opportunity, but another opportunity to make sure, if there's anything else that's missing from the model that ought to be part of this discussion, we should bring them up now. I want to make it clear that the use of the model was intended to facilitate a broader conversation, not to be the entire focus of the conversation, and that's why these questions are here, to make sure if there's other issues that we have a chance to put them on the table.
DR. PAPATHEOFANIS: Let me take Sally first, and then Barbara and then we will get to Peter.
MS. HART: Well, this isn't exactly another issue but it's another consideration, and I'm speaking about the concern that there could be harm to people in getting an accurate diagnosis in the sense of their being labeled or losing employment opportunities or insurability and the consideration that we haven't discussed I think is the option for an individual to decline to be tested if they are concerned about those factors.
DR. PAPATHEOFANIS: Barbara?
DR. McNEIL: Well, I'm not going to verbalize this well but I think it may apply to lots

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of other studies that we do, and I think it came up a little bit in our previous discussion. None of our models talk about the differential value of certain kinds of doctors in starting off the whole diagnostic

and therapeutic process, so it's conceivable that a model could be built, and I don't think we should in this case because I haven't seen enough evidence to show that, but that it could start back and say patient comes in with symptoms of some sort and then the question is do you follow on to treat X based on that doctor's prior probabilities which then feed into the remainder of the tree? Or instead, do you send that patient to Dr. Y who has a much higher performance set of characteristics and then move along the same tree.
That is assessing the technology in the environment in which the system functions and the patient is cared for, and that would really expand enormously. I'm not suggesting we do it here, but you asked what other issues are not addressed in this model. In fact, that's an issue that's not addressed in most of the current decision analytic models, for cardiac disease, for cancer, for any of them, so the same thing would apply here.
DR. PAPATHEOFANIS: Good point.

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Dr. Conti.
DR. CONTI: Just to make a couple comments also on the model. I'm sitting here listening to some of this discussion and I agree with a lot of what's being said on both sides of the fence, but I'm also worried that this is a new model, it's a new approach, and I'm wondering perhaps whether we're using it prematurely in the decision process. From what I heard, it's never been sort ot tested, if you will, in this type of forum. And is it appropriate for the panel to make a decision on efficacy of a radiopharmaceutical in this case, for PET scanning, on the basis of an unproven model? Just something to think about.
The model doesn't take into account a couple of things also that I was concerned about, and one of the things for example is the timing of therapy. We heard some evidence today that the timing of therapy could influence the outcome. Does the model adequately deal with when the final go is

given to treat the patient if we're going to treat all, when is that decision made? Is it made after the first assessment, is it made after six months, is it a year, and are we potentially losing ground in those patients if we delay.

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This is a dynamic field. We picked acetylcholinesterase inhibitors. Six months from now, maybe it's Valium, I don't know. But the reality is that drug development is going to go on, so we're going to have to deal with a model that takes into account the full spectrum of the benefits as well as the side effects, and whether the test indicates it would be beneficial if the side effects increased. I think you really need to think about that, and take that spectrum into consideration to determine whether or not the test is helpful in the management of patients, not just the specific drug or type of drugs.

Clinical trials are going to require improved diagnostic accuracy, they do require the best diagnostic accuracy as far as entrance criteria. How can we sit here and say that it's okay to use a technique that's less accurate for patients to enter clinical trials? Drug development, the NIH would frown on that obviously. PET offers an improved diagnostic accuracy, both models conclude that, so why aren't we using that to enter these patients into clinical trials for future drug development.

Now the issue of the accuracy of the outcome data is also affected by which patients you

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send to those trials. So if you preselect with a tighter criteria you are more likely to have more reliable outcome data upon which to base future decisions and improve your models.

The polydrug issue and compliance. From a practical point of view, I remember my grandmother having difficulty timing which medication she took at which time. It may be okay to remember when to take your acetylcholinesterase inhibitor, but when you

have five or six drugs, compliance is going to go down, that's just the practical side of it. I don't have data to show you, I just have practical experience and I think everyone in this room probably has the same practical experience.

So, I think those are the key things I want to mention on the modeling and I think we need to really, if we're going to consider the fact that this is a new way of looking at this, maybe we ought to be thinking of relying more on our traditional standards, is the test better or equivalent to what's currently available, as opposed to speculating which model is going to do which things and what the assumptions are, whether they are valid or not.

DR. PAPATHEOFANIS: Let me, before I continue on, just briefly give my short-term memory a

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run of things. Just to respond to Dr. Conti and folks in the audience who have very similar questions, I think in this case we're thinking of modeling as fundamental to the technology assessment policy or technology assessment process. I don't think that anyone should come away feeling that this modeling is in any way experimental, apart from the fact that there are assumptions that have to be made and it's not unlike what folks do in the laboratory when they make assumptions in doing experimental research. The methodologies continue to be worked out, but one should keep in mind that very significant decisions at multilevels in many different industries, many different areas, rely on decision analysis and decision modeling to help them work their way through very complex issues. I think that part of the challenge here is that we are not only looking at a disease process that's complex in its current state if you will, but a disease process that's chronic, and once you enter into the notion of chronicity, it becomes extremely difficult to determine or answer questions such as when does one enter treatment and when is that person entered into the model.

I'm sure Dr. Matchar could create tracker

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variables and do whatever else he has to do to answer questions like that, but I think that that's not really what we were asking of this model. What we wanted was some assistance in clarifying this complex issue and then it turns out the model was the way to get that assistance, and then once we had the model, we obtained expert assistance from folks who are as experienced or more experienced than the members of this panel. So I think the process has been as rigorous and as appropriate as we can make it. I don't think that anyone would argue that the use of PET imaging in clinical trials would be contradictory to anything we're saying here, that clinical trial and the use of novel not only experimental techniques but also the diagnostic components that go with them are open to the clinical trialists in the designs that they come up with and the sponsoring institutions, and I don't think we have said anything here that prevents anyone from using PET in any sort of clinical trial. I think what we're trying to develop is this notion of are we comfortable looking at this complex process using a fairly complex methodology and can we make a decision based on what we have. So, enough editorializing from me, but I just wanted to sort of summarize and

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move on with that.
The third point under our general discussion is the notion, one that we really haven't addressed very keenly, and that is can PET serve as a replacement for rather than an adjunct to the existing approaches or conventional clinical evaluation for suspected Alzheimer's dementia. I wanted to spend a little bit of time here and a little bit of discussion here, especially with some of our clinical experts who have hands-on experience in these areas. Marilyn, I always look at you.
DR. ALBERT: I don't know that we actually have much data on this question. Most of the studies that I know of take people who have already been

worked up with a clinical evaluation and then see whether or not you can accurately identify them or more accurately identify them. I don't myself know of any studies that have for instance taken everybody in a primary care practice without an evaluation and done a scan.
DR. PAPATHEOFANIS: Dr. Johnson.
DR. JOHNSON: I'm not aware of any such data. It's a really important question. To some extent when I was reviewing this, I was puzzled by the implication that the structure of this enterprise

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is that we're looking at one technology against a backdrop of the traditional application of a whole family of things in the setting basically of a neurologist's office. And it made we wonder, how good is the information about that. How much do we know about that in terms of accuracy and so forth? So I think it's a very important question.
DR. PAPATHEOFANIS: What's your I guess at this point, highly educated guess regarding replacement or identifying it as a technology that could replace versus serve as an adjunct to?
DR. JOHNSON: I think this frequently comes up in neurologic practice when a new technology of any sort comes in from another discipline, and it was true in the case of CT scanning and certainly in the case of various forms of MRI. Again, as Marilyn has pointed out, there is no data and such a study would be a very important thing to do but very difficult to do.
DR. ALBERT: I think it's also worth adding that when imaging techniques, sophisticated imaging techniques became available, the original hope was that these tools would be the tests that you could give and you could eliminate the clinical evaluation, and so far people have been disappointed

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in the ability to do that with a particular test. I think right now the consensus is that maybe if you had a combination of tests you could do that, but

that's not based on any data.
DR. PAPATHEOFANIS: Peter.
DR. NEUMANN: Those are both excellent points. I would just add, to some extent the model considers such eventualities in the sense that there are extensive sensitivity analysis on the prevalence. So if you believe that first standard workup is much more accurate, PET won't look as good, and if you believe it's much less accurate, it will look better, but you can sort of infer from the sensitivity analysis what's going on.
DR. PAPATHEOFANIS: Excellent point. Sean, did you want to ask any more questions?
DR. TUNIS: Maybe since we didn't get open public responses much before, to give one last chance for anyone to offer comments before we move to the voting question.
DR. PAPATHEOFANIS: So are you pretty comfortable then with the discussion on questions 1, 2 and 3 at this point?
DR. TUNIS: Yeah, I am. I would just ask Dr. Burken or Dr. Furo, do you want to pursue any of

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those questions any further?
DR. BURKEN: Just revisiting question 2, Dr. Papatheofanis, and this is just a matter of protocol, were we going to run through the whole group and have them comment on question number 2?
DR. PAPATHEOFANIS: No.
DR. BURKEN: Okay, thank you.
DR. PAPATHEOFANIS: Let's make available about ten minutes for any additional public comment. Feel free to step up to the podium and either ask us questions, or we can ask you some questions.
MS. LATELLE: My name is Candace Latelle with Latelle and Associates. This is probably beyond the purview of this group but I thought I might raise it, perhaps when CMS looks at the broader coverage decision associated with this discussion, and that is as I understand it, these drugs that are being looked at under the treat all scenario are self administered drugs and therefore, they would not be part of

covered services for Medicare beneficiaries. And whether or not there is value in a rule-out associated with a PET scan that would then eliminate cost to the beneficiary of not taking those drugs. So again, it's not pertaining specifically to the model, but I think it does deal with the broader

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coverage question that this model and this discussion will be used for, and that is the exposure of Medicare beneficiaries to increased costs, or the potential for PET to reduce some of those costs in terms of the cost of self administered drugs.
DR. TUNIS: Making any comment about payment for outpatient drugs or costs in the context of coverage really is beyond what I'm willing to talk much about, but those are good points.
DR. PAPATHEOFANIS: Right. And also kind of bringing it all the way back, I think that we are not making a recommendation to the American Academy of Neurology, we're not making a recommendation on changing practice guidelines, we are basically reviewing a model as I said, which we use as a tool in helping us to make a decision. Any other public comment?
MS. ANDERSON: For the record, the voting members today are Barbara McNeil, Carole Flamm, Jeffrey Lerner, Kim Burcheil, Steven Guyton, and Chairperson Frank Papatheofanis will vote in the event of a tie. A quorum is present. Now I will ask someone from the panel to give us a motion to vote on today's voting question.
DR. LERNER: So move.

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MS. ANDERSON: And I need a second.
DR. GUYTON: Second.
MS. ANDERSON: Okay, I'm going to read the voting question. Is the evidence adequate to demonstrate that PET has clinical benefit in evaluating patients with suspected AD?
DR. TUNIS: Can I ask a question for clarification of the question? And this may be a

question for Dr. Burken again, and sorry to have gotten this far without being clear on this, but we've talked today and there have been the three model scenarios for mild to moderate dementia, mold cognitive impairment, and suspected or family history, I guess. Does the suspected Alzheimer's disease encompass all three of those categories together, is that the way the question was intended, would there be -- can you.
SPEAKER: It would include the category of probable Alzheimer's, potentially could include symptoms, mild symptoms. It would not include the asymptomatic.
DR. TUNIS: One of the reasons, it seems to me that as we got into parsing the discussion about the different scenarios in the model that the model as it applied to mild to moderate dementia for

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the treat all strategy, that treat all strategy is the gold standard clinical approach, it's the FDA approved use of the drug for mild to moderate dementia, so that the treat all strategy there represents something that is clinically defensible and not speculative. For the mild cognitive impairment it is actually a somewhat different question, because the treat all strategy there has the large caveat of if one believed that the treatment was effective for that population, which strategy would then dominate. And I guess the committee is free to vote on these two questions together, but we also I suppose could consider a separate vote as it relates to mild to moderate dementia, one scenario, and the mild cognitive impairment, which is a different scenario that seems like it has some different characteristics.
DR. GUYTON: So in effect though, that second point would endorse an unproven treatment strategy is what you're saying, for MCI. Even though that's not what we're doing, still there is an implication there that that's better than getting a PET scan, by this panel. Is that not right?
DR. TUNIS: I guess if you were to vote in

the affirmative for that, you would be endorsing an

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unproven treatment strategy. Is that what you mean.
DR. BURCHEIL: Well, I took from what Dr. Matchar said was we need to be very careful to differentiate the scenario A from everything else. And I think from what he said, that was the only implication of the model, although it's a little bit fuzzy because there are these other things out there which were sort of, at no extra charge we'll throw in B and C. But I think this middle ground is crucial because that gets into this issue I was talking about of unproven therapies.
DR. PAPATHEOFANIS: Should we modify the voting question then to only include the scenario A? Can we do something like that and satisfy what you need, Sean, or do you really want to try to break it into those two?
DR. TUNIS: It might be based on some of this discussion that the committee would actually like to answer a different question characterizing suspected Alzheimer's disease slightly differently, as in the mild to moderate dementia.
DR. BURCHEIL: I would like to make a motion. I would move that we vote on Alzheimer's as defined by scenario A, which is proven or probable Alzheimer's, and not vote on MCI. Maybe one of the

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neurologists can give a better framework for that, basically voting for Alzheimer's and not the second category.
DR. JOHNSON: I guess you would have to specify what exactly you mean and what definition.
DR. BURCHEIL: Using the AAN definitions.
DR. PAPATHEOFANIS: Scenario B basically.
DR. BURCHEIL: Yeah, staying away from scenario B.
DR. PAPATHEOFANIS: Right. And not having a recommendation based on something that isn't happening right now, and having someone misconstrue that as a clinical recommendation.

DR. PAPATHEOFANIS: We have a motion and do we have a second.
DR. LERNER: I assume I should withdraw.
DR. PAPATHEOFANIS: Okay. Do you have a recommendation? So now the motion on the table is Dr. Burcheil's. Do you have any recommendation on how we can change that language, do we just add a couple of words that say as specified in scenario A.
DR. BURCHEIL: Or as defined by the AAN would probably be better; no one is going to understand what scenario A is outside of this room.
DR. PAPATHEOFANIS: Right, but I mean, the

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substance of scenario A.
DR. BURCHEIL: Scenario A is effectively those guidelines if I understand that correctly, is that not right?
DR. MATCHAR: Yes, scenario A is individuals with functional impairment and therefore, satisfy the criteria for dementia. And the only reason that B is being separated out is because of the absence of evidence about clinical efficacy of treatment in that scenario. However, my understanding is that that was the question that was being raised by the advocates of the PET scanning technology.
DR. BURCHEIL: Can I also point out, though, that the advocates, and maybe they want to respond, for MCI they have no outcome data either to put forward, all they have is specificity and sensitivity data. Is that correct for MCI?
DR. SILVERMAN: Outcome data using drugs per se?
DR. BURCHEIL: Yeah, for treatment outcome.
DR. SILVERMAN: Right, outcome data would be based on treating patients who have, as FDA says, mild to moderate Alzheimer's, but changing what that

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means to include the diagnosis made with the inclusion of PET, along with the standard AAN

criteria. Otherwise, you'd never be able to evaluate any new test that wasn't already there.
DR. BURCHEIL: I think I'm talking specifically about MCI.
DR. SILVERMAN: That's what I'm saying. MCI includes people who do have Alzheimer's and people who don't have Alzheimer's, but without PET, there is no way to distinguish those two groups. If you interpret the FDA label that it is used in people with mild to moderate Alzheimer's, that MCI actually includes some people who have mild Alzheimer's, but before PET there was no way to find those people, then we would say there is outcome data, yes.
DR. PAPATHEOFANIS: Well, Janet's going to read off --
DR. ALBERT: Just to say that right now, there are trials underway with patients who meet criteria for MCI with these cholinesterase inhibitors, and they are not yet complete.
DR. SILVERMAN: Right, but those trials still won't answer the question. The question is, among those patients with MCI who PET says have Alzheimer's, will they benefit. And there we can

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just turn to the FDA label and whether or not people believe that PET says they have Alzheimer's, it is more likely they do have Alzheimer's.
DR. PAPATHEOFANIS: Okay. Janet is going to read out a very carefully word smithed modification.
MS. ANDERSON: I'm reading this for the purpose of making sure that this is indeed Dr. Burcheil's motion, and then we'll get a second and then we'll vote.
Is the evidence adequate to demonstrate that PET has clinical benefit in evaluating patients with suspected AD as defined by the American Academy of Neurology guidelines?
DR. BURCHEIL: Is suspected the right word then, because is that the wording in the guidelines?
DR. ALBERT: It must be probable and possible AD, is it not?

DR. ANDERSON: It's your motion, Dr. Burcheil.
DR. BURCHEIL: I'm asking for help from my neurology colleagues here.
SPEAKER: There is a member of the committee of the AAN here, you can ask him.
DR. ALBERT: I am assuming the language is

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the same as the NIN/CDS/ADRA criteria, which is probable and possible, but I'm just trying to find it.
DR. PAPATHEOFANIS: Not to put you on the spot, but do you know the exact wording?
DR. SMALL: I have the entire transcript of the deliberations of the committee in my head. I'm trying to understand what the issues are here. You know, we talk about several terms that can be used. You can talk about questionable dementia, you can talk about possible dementia, and you can talk about probable Alzheimer's disease. I think what we said already, if somebody has probable Alzheimer's disease, you're pretty convinced of the diagnosis, and PET may not be helpful or necessary, it may be something extra. So to use the term suspected dementia, I don't believe that there are actual operational criteria for that.
I mean, we're kind of talking about this area where people have cognitive symptoms. Basically, what is the cut point? When we say dementia, what's the difference between dementia and MCI, the basic difference is the person's ability to function. And that's one of the basic differences because you have with MCI primarily a memory

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impairment that is quite similar to someone with early dementia but they are still functioning in the community. So I think it gets to be when you talk about a suspected dementia, that could be someone who has MCI, you're not quite sure if there is functional impairment, it's this gray zone that I think is very difficult to pin down.

I think if you went through the AAN documents, I don't know that you'd get the answer to that. I think my question would be, what's behind the concern in the word smithing? Is the concern that you're going to make a recommendation that people should be treated outside the FDA indications? My understanding was this panel was not making treatment recommendations, all you're doing is judging the technology in terms of its added value in the diagnosis.
DR. ALBERT: We have the guidelines here and my reading of it indicates that they use the term dementia to refer to what is then defined in the DSM-IIIR, the DSM-IV or the NIN/CDS/ADRA criteria, all of which use the terms possible and probable AD, not suspected AD.
DR. SMALL: Right. And possible AD, as I recall from the NIN/CDS/ADRA criteria, means that

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there is a dementia but it's possible that there could be several different causes, or could be something -- no?
DR. ALBERT: No.
DR. SMALL: It doesn't mean questionable?
DR. ALBERT: No. It means that someone has a dementia and it's possible that some other medical condition might be --
DR. SMALL: Exactly. That's what I mean, but there is a dementia, it's not a questionable dementia.
DR. ALBERT: That's correct.
DR. SMALL: It's not MCI.
DR. ALBERT: Yes, that's correct.
DR. PAPATHEOFANIS: Well, a suggestion on word smithing would be, so, are you recommending then in the wording of the voting question we change the word suspected to possible or probable AD?
DR. ALBERT: I think so.
DR. PAPATHEOFANIS: Kim?
DR. BURCHEIL: I'm just trying to differentiate this from MCI so we don't sort of overstep where there's very little information.

DR. PAPATHEOFANIS: Would you prefer possible or probable?

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DR. BURCHEIL: I think you have to put both.
DR. ALBERT: I think in practice it's possible and probable.
DR. PAPATHEOFANIS: I agree. So then the voting question if you agree, Kim, that's on the table, has been changes to: Is the evidence adequate to demonstrate that PET has clinical benefit in evaluating patients with possible or probable AD as defined by the AAN guidelines.
DR. BURCHEIL: Right.
DR. LERNER: Could you add the word current AAN guidelines?
DR. PAPATHEOFANIS: Sure, by current AAN guidelines. You're right, and that's an important point actually. Are you comfortable with that, Kim?
DR. BURCHEIL: Yes.
MS. ANDERSON: We need a second on this motion.
DR. McNEIL: Second.
MS. ANDERSON: And we will vote. All those voting for the motion? All those voting against the motion?
(Inaudible colloquy.)
MS. ANDERSON: Okay. The motion is to

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vote on the following question: Is the evidence adequate to demonstrate that PET has clinical benefit in evaluating patients with possible or probable AD as defined by current American Academy of Neurology guidelines?
DR. McNEIL: I'm sorry. Are we answering this question or are we voting on a motion to make this the question?
MS. ANDERSON: I thought that we only had one motion.
THE REPORTER: Dr. Burcheil moved to vote on that question, it was seconded, so that is what's

before the panel.
DR. McNEIL: So we're voting on this, yes or no.
DR. PAPATHEOFANIS: Correct.
MS. ANDERSON: Those voting yes?
DR. TUNIS: Yes meaning yes, the evidence is sufficient.
(No response.)
MS. ANDERSON: Those voting no, or against the motion?
(All voting members raised their hands.)
MS. ANDERSON: We don't have any abstaining, to the vote is against, and it's

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unanimous.
DR. TUNIS: So, just to tie a loop related to, since we altered the original voting question somewhat, what we left on the table at least in my mind but you can tell me how you want to dispense with it, is the issue of mild cognitive impairment, and whether you are as a panel not wanting to vote on that question, or can we potentially have a motion on that question and vote on it separately. Or would you argue that if you voted no on the sufficiency of evidence for possible or probable Alzheimer's disease, automatically the evidence is insufficient for mild cognitive impairment? Any comment on that?
DR. McNEIL: Sean, I have one comment. That's why I actually wanted to see the criteria that we were using. So if we're using those criteria in that we have to consider both of them, and if part of the second one is based on an off-label use or an unapproved FDA use, then I think we're in a situation where we can't really follow the guidelines that we made for ourselves because of the non-FDA approval of the drug as I understand it, for mild cognitive impairment. In other words, because it's not approved, are we allowed to look at evidence that would be based on health outcomes? If we are

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allowed, then I would be able to vote on it.

DR. TUNIS: Yeah. It is an FDA approved drug, this would be an off-label use of an FDA approved drug, which is legal. This committee does not have the authorization to make binding recommendations on clinical practice. So the answer is, you can consider it, you are not precluded from considering it. You know, you may take the fact that it's not FDA approved for this indication as part of your deliberation, but you don't get off from having to think about it just because it's not FDA approved. So I guess that's the way I would answer that.
DR. PAPATHEOFANIS: So the question is do we take a second vote on the MCI application of this question? Do we just recast or rephrase this to indicate the MCI application, that would be the most straightforward, right?
DR. BURCHEIL: I think we should, because I think this is going to come up and we should be on the record for that. It's obviously a very important point and we could abstain, but it leaves a little doubt as to what the panel had.
DR. PAPATHEOFANIS: Okay. So I need another motion.
DR. BURCHEIL: I would move that we amend

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the question for this next vote to just read mild cognitive impairment instead of AD, using the same verbiage.
DR. PAPATHEOFANIS: Okay. Janet is going to compose that and read that to you before a vote is taken on that.
DR. TUNIS: Is Dr. Silverman still here?
DR. SILVERMAN: Yes.
DR. TUNIS: In regards to this, there was a comment that you made about ten minutes ago or so where it sounded as if you were suggesting that the use of PET in patients with mild cognitive impairment might in fact identify a subgroup who one might then identify as having probable Alzheimer's disease by virtue of the PET findings and who would then qualify for treatment. Did I get that right and is that our argument?

DR. SILVERMAN: That's almost right. I wouldn't use the words probably Alzheimer's, that has a very specific definition as assigned by NIN/CDS/ADRA, but that they actually probably have Alzheimer's is what we would say. And there's also a hole that's being left here, if you consider just MCI and just possible and probably AD, because there are many people who have dementia who would qualify by

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DSM-III or DSM-IV criteria as having dementia who still wouldn't have possible Alzheimer's or probable Alzheimer's. You might think that they have dementia and you might say I know they have vascular disease, and the PET scan might show in fact that they have Alzheimer's disease on top of their vascular disease, so the people who have possible or probable AD don't include all the people who have dementia, those are two issues that are being confused here, or at least there's still a gap of people who aren't being considered by the decision that's being made here.
DR. PAPATHEOFANIS: Let's hear the redrafted question.
MS. ANDERSON: I'm going to read the question and then I'm going to ask for a motion. The question reads: Is the evidence adequate to demonstrate that PET has clinical benefit in evaluating patients with mild cognitive impairment as defined by current AAN guidelines? A motion to vote please?
DR. McNEIL: So move.
MS. ANDERSON: I need a second.
DR. FLAMM: Second.
MS. ANDERSON: To the question that I just read, anyone voting yes, or for the question?

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(No response.)
MS. ANDERSON: Anyone voting no, or against the question?
(All voting members raised their hands.)
MS. ANDERSON: No one abstaining. We have a unanimous vote against.

DR. TUNIS: So provoked again by that last comment by Dr. Silverman, we don't want to leave any holes here, so we have now voted on this mild to moderate, or the possible or probable Alzheimer's disease and we voted on mild cognitive impairment. It's possible that we had actually wanted to vote on this broader category of the dementia that Dr. Silverman just talked about when we did the first vote, I don't know. Let's address it at least because otherwise we will be haunted by it to the end of our days.
DR. SILVERMAN: Since I provoked it, can I suggest an alternative, that you vote, rather than include that in the original, that you just vote on that as a third category right now, that people who meet the category of dementia but don't meet the category of possible or probable Alzheimer's disease by NIN/CDS/ADRA criteria?
DR. ALBERT: We haven't heard any data

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about that.
DR. TUNIS: Because unfortunately, I guess Dr. Matchar has left, but Deb, scenario A or whatever the heck it was --
DR. ZARIN: You're talking about people who have dementia and by the AAN criteria don't have probable or possible AD, you're saying have some other cause of dementia, but the argument is they might also have AD?
DR. SILVERMAN: That's correct.
DR. ZARIN: I guess conceptually you could think of that as a different, as a lower prior probability in your sensitivity analysis. I mean, that's the only way I can think of the model applying to that group. They'd have some probability of AD that's less than the probable AD group that's higher than zero is the argument, and if you recall those sensitive analyses, as the prior probability goes down, you would have to pull it out, but I guess -- let me say that besides applying the model, I don't know of any test accuracy data on PET scans in that group, so I would think that the first bullet

wouldn't -- I mean as far as I know, there is no data on what the operating characteristics of PET would be in that group, so I don't think you can go beyond

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that. Forget about what I said about trying to apply the model, I don't think you could even get there. By your look I don't think what I said helped.
DR. TUNIS: It all helps.
DR. GUYTON: I would move that we proceed on toward adjournment without any further motions.
DR. TUNIS: I don't think that's an appropriate motion yet.
DR. PAPATHEOFANIS: So, what's the bottom line, do we take a third vote.
MS. ANDERSON: If there's no motion, then there's no vote.
DR. PAPATHEOFANIS: Okay, no motion, no vote. Are you okay with that or is that going to leave you hanging?
DR. TUNIS: I'm okay with that.
DR. PAPATHEOFANIS: What's next on the agenda, panel business.
MS. ANDERSON: I think we did it. If Sean has anything else he wanted to add in addition to his previous comments this morning.
DR. TUNIS: No. I would just point out, first of all, thank the panel and all the guests and our presenters for their good work, and also point out that we are still formally operating under the

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rules for the MCAC that this recommendation will have to be forwarded to the Executive Committee. There has not yet been a statutory or regulatory change that allows this panel to directly recommend to CMS. There is an Executive Committee meeting scheduled I believe it's April 16th, so that's when this will go before the Executive Committee. And other than that, just thanks again for your assistance.
DR. PAPATHEOFANIS: Let me also add my thanks again, especially to the three ad hoc members who behind the scenes and also today have helped

other members of this committee arrive at some very reasonable conclusions and make some recommendations. I would also like to thank Janet Anderson for all her help, and I think with that --

MS. ANDERSON: One last thing before we go. For continuing information, you can visit our web site at www.cms.hhs.gov\coverage, or there is a coverage process button on the cms.hhs.gov web site. To conclude today's session, would someone move that this meeting be adjourned.

DR. GUYTON: So move.

MS. ANDERSON: A second?

DR. LERNER: Second.

MS. ANDERSON: Thanks everyone, the

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meeting is adjourned.

(The meeting adjourned at 2:20 p.m.)